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(54) Title: NOVEL SERINE PROTEASE INHIBITOR NUCLEIC ACID MOLECULES, PROTEINS AND USES THEREOF

(57) Abstract

The present invention relates to flea serine protease inhibitor proteins; to flea serine protease inhibitor nucleic acid molecules, including those that encode such serine protease inhibitor proteins; to antibodies raised against such serine protease inhibitor proteins; and to compounds that inhibit flea serine protease inhibitor activity. The present invention also includes methods to obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to protect animals from hematophagous ectoparasite infestation.

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NOVEL SERINE PROTEASE INHIBITOR NUCLEIC ACID MOLECULES, PROTEINS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to flea serine protease inhibitor nucleic acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised against such proteins, and inhibitors of such proteins. The present invention also includes therapeutic compositions comprising such nucleic acid molecules, proteins, antibodies, and/or other inhibitors, as well as their use to protect an animal from flea infestation.

BACKGROUND OF THE INVENTION

Hematophagous ectoparasite infestation of animals is a health and economic concern because hematophagous ectoparasites are known to cause and/or transmit a variety of diseases. Hematophagous ectoparasites directly cause a variety of diseases, including allergies, and also carry a variety of infectious agents including, but not limited to, endoparasites (e.g., nematodes, cestodes, trematodes and protozoa), bacteria and viruses. In particular, the bites of hematophagous ectoparasites are a problem for animals maintained as pets because the infestation becomes a source of annoyance not only for the pet but also for the pet owner who may find his or her home generally contaminated with insects. As such, hematophagous ectoparasites are a problem not only when they are on an animal but also when they are in the general environment of the animal.

Bites from hematophagous ectoparasites are a particular problem because they not only can lead to disease transmission but also can cause a hypersensitive response in animals which is manifested as disease. For example, bites from fleas can cause an allergic disease called flea allergic (or allergy) dermatitis (FAD). A hypersensitive response in animals typically results in localized tissue inflammation and damage, causing substantial discomfort to the animal.

The medical importance of hematophagous ectoparasite infestation has prompted the development of reagents capable of controlling hematophagous ectoparasite infestation. Commonly encountered methods to control hematophagous ectoparasite infestation are generally focused on use of insecticides. While some of these products are efficacious, most offer protection of a very limited duration at best. Furthermore,

many of the methods are often not successful in reducing hematophagous ectoparasite populations. In particular, insecticides have been used to prevent hematophagous ectoparasite infestation of animals by adding such insecticides to shampoos, powders, sprays, foggers, collars and liquid bath treatments (i.e., dips). Reduction of hematophagous ectoparasite infestation on the pet has been unsuccessful for one or more of the following reasons: (1) failure of owner compliance (frequent administration is required); (2) behavioral or physiological intolerance of the pet to the pesticide product or means of administration; and (3) the emergence of hematophagous ectoparasite populations resistant to the prescribed dose of pesticide.

Prior investigators have described sequences of a few insect serine protease inhibitors: *Bombyx mori* nucleic acid and amino acid sequences have been disclosed by Narumi et al., *Eur. J. Biochem.*, 214:181-187, 1993; Takagi et al., *J. Biochem.*, 108:372-378, 1990; and amino acid sequence has been disclosed by Sasaki, *Eur. J Biochem*, 202:255-261, 1991. *Manduca sexta* nucleic acid and amino acid sequences have been disclosed by Kanost et al., *J. Biol. Chem*, 264:965-972, 1989; U.S. Patent No. 5,436,392, to Thomas et al., issued July 25,-2085, 1990; U.S. Patent No. 5,196,304, to Kanost et al., issued March 23, 1993; Jiang et al., *J. Biol. Chem.*, 269:55-58, 1994; and *Manduca sexta* peptide sequences have been disclosed by Fox et al., *Peptides*, 12:937-944, 1991. *Locusta migratoria* peptide sequences have been disclosed by Kellenberger et al., *J. Biol. Chem*, 270:25514-25519, 1995. *Rhodnius prolixus* peptide sequences have been disclosed by Van De Locht, *EMBO*, 14:5149-5157, 1995. *Lymantria dispar* peptide sequences have been disclosed by Valaitis, *Insect Biochem Molec Biol*, 25:139-149, 1995. *Lucilia cuprina* nucleic acid and amino acid sequences have been disclosed by Casu et al., *Insect Molecular Biology*, 3:159-170, 1994. Identification of a serine protease inhibitor of the present invention is unexpected because the most identical amino acid or nucleic acid sequence identified by previous investigators could not be used to identify a flea serine protease inhibitor of the present invention.

In summary, there remains a need to develop a reagent and a method to protect animals from hematophagous ectoparasite infestation.

SUMMARY OF THE INVENTION

The present invention relates to a novel product and process for protection of animals from hematophagous ectoparasite infestation. According to the present invention there are provided flea serine protease inhibitor proteins and mimetopes thereof; flea nucleic acid molecules, including those that encode such proteins; antibodies raised against such serine protease inhibitor proteins (i.e., anti-flea serine protease inhibitor antibodies); and other compounds that inhibit flea serine protease inhibitor activity (i.e, inhibitory compounds or inhibitors).

The present invention also includes methods to obtain such proteins, mimetopes, nucleic acid molecules, antibodies and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, mimetopes, nucleic acid molecules, antibodies, and/or inhibitory compounds, as well as use of such therapeutic compositions to protect animals from hematophagous ectoparasite infestation.

Identification of a serine protease inhibitor protein of the present invention is unexpected because the most identical amino acid or nucleic acid sequence identified by previous investigators could not be used to identify a flea serine protease inhibitor protein of the present invention. In addition, identification of a flea serine protease inhibitor protein of the present invention is unexpected because a protein fraction from flea prepupal larvae that was obtained by monitoring for carboxylesterase activity surprisingly also contained flea serine protease inhibitor molecular epitopes of the present invention.

One embodiment of the present invention is an isolated flea serine protease nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene, including, but not limited to, nucleic acid molecules that hybridize under stringent conditions with a nucleic acid molecule having at least one of the following nucleic acid sequences:SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID

NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90. Particularly preferred flea serine protease inhibitor nucleic acid molecules include nucleic acid sequences SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, and/or nucleic acid sequences encoding proteins having amino acid sequences SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, as well as allelic variants of any of the listed nucleic acid sequences or complements of any of the listed nucleic acid sequences.

The present invention also includes an isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid sequence encoding a protein comprising an amino acid sequence including SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID

NO:89, SEQ ID NO:90, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO: 97, and SEQ ID NO:98.

The present invention also relates to recombinant molecules, recombinant viruses and recombinant cells that include flea serine protease inhibitor nucleic acid molecules of the present invention. Also included are methods to produce such nucleic acid molecules, recombinant molecules, recombinant viruses and recombinant cells.

Another embodiment of the present invention includes an isolated flea serine protease inhibitor protein. A preferred flea serine protease inhibitor protein is capable of eliciting an immune response when administered to an animal and/or of having serine protease inhibitor activity. A preferred flea serine protease inhibitor protein is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a nucleic acid sequence including SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:21, SEQ ID NO:27, and SEQ ID NO:33, SEQ ID NO:47, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:56, SEQ ID NO:59, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:68 and SEQ ID NO:71. Particularly preferred flea serine protease inhibitor proteins include at least one of the following amino acid sequences: SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO: 97, and SEQ ID NO:98.

Yet another embodiment of the present invention is a therapeutic composition that is capable of reducing hematophagous ectoparasite infestation. Such a therapeutic composition includes one or more of the following protective compounds: an isolated flea serine protease inhibitor protein or a mimetope thereof; an isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene; an isolated antibody that selectively binds to a flea *Ctenocephalides felis* serine protease inhibitor protein; and an inhibitor of serine protease inhibitor protein activity identified by its ability to inhibit flea serine protease inhibitor activity, such as, but not limited to, a substrate analog of a flea serine

protease inhibitor protein. A preferred therapeutic composition of the present invention also includes an excipient, an adjuvant and/or a carrier. Also included in the present invention is a method to reduce flea infestation. The method includes the step of administering to the animal a therapeutic composition of the present invention.

The present invention also includes an inhibitor of serine protease inhibitor protein activity identified by its ability to inhibit the activity of a flea serine protease inhibitor protein. An example of such an inhibitor is a substrate analog of a flea serine protease inhibitor protein. Also included in the present invention are mimetopes of flea serine protease inhibitor proteins of the present invention identified by their ability to inhibit flea serine protease activity.

Yet another embodiment of the present invention is a method to identify a compound capable of inhibiting flea serine protease inhibitor activity. The method includes the steps of: (a) contacting an isolated flea serine protease inhibitor protein with a putative inhibitory compound under conditions in which, in the absence of the compound, the protein has serine protease inhibitor activity; and (b) determining if the putative inhibitory compound inhibits the activity. Also included in the present invention is a test kit to identify a compound capable of inhibiting flea serine protease inhibitor activity. Such a kit includes an isolated flea serine protease inhibitor protein having serine protease inhibitor activity and a means for determining the extent of inhibition of the activity in the presence of a putative inhibitory compound.

Yet another embodiment of the present invention is a method to produce a flea serine protease inhibitor protein, the method comprising culturing a cell transformed with a nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 depicts proteins from tissue extracts that bind to a polyclonal antiserum made against a serine protease inhibitor protein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for isolated flea serine protease inhibitor (SPI) proteins, isolated flea serine protease inhibitor nucleic acid molecules, antibodies directed against flea serine protease inhibitor proteins and other inhibitors of flea serine

protease inhibitor activity. As used herein, the terms isolated flea serine protease inhibitor proteins and isolated flea serine protease inhibitor nucleic acid molecules refers to serine protease inhibitor proteins and serine protease inhibitor nucleic acid molecules derived from fleas and, as such, can be obtained from their natural source or can be produced using, for example, recombinant nucleic acid technology or chemical synthesis. A SPI protein can have the ability to inhibit the proteolytic activity of a serine protease protein. A protein denoted as a SPI protein can also possess cysteine protease activity, in addition to serine protease activity. Also included in the present invention is the use of these proteins, nucleic acid molecules, antibodies and other inhibitors as therapeutic compositions to protect animals from hematophagous ectoparasite infestation as well as in other applications, such as those disclosed below.

Flea serine protease inhibitor proteins and nucleic acid molecules of the present invention have utility because they represent novel targets for anti-hematophagous ectoparasite vaccines and drugs. The products and processes of the present invention are advantageous because they enable the inhibition of hematophagous ectoparasite serine protease activity necessary for hematophagous ectoparasite survival or the inhibition of serine protease inhibitors, thereby deregulating serine protease activity, leading to uncontrolled proteolysis of an hematophagous ectoparasite.

One embodiment of the present invention is an isolated protein comprising a flea SPI protein. It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, a protein refers to one or more proteins or at least one protein. As such, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. Furthermore, a compound "selected from the group consisting of" refers to one or more of the compounds in the list that follows, including mixtures (i.e., combinations) of two or more of the compounds. According to the present invention, an isolated, or biologically pure, protein, is a protein that has been removed from its natural milieu. As such, "isolated" and "biologically pure" do not necessarily reflect the extent to which the protein has been purified. An isolated protein of the present invention can be obtained from its natural source, can be produced using recombinant DNA technology or can be produced by chemical synthesis.

As used herein, an isolated flea SPI protein can be a full-length protein or any homolog of such a protein. An isolated protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response against flea SPI proteins and/or ability to inhibit, or reduce, serine protease activity. Examples of serine protease inhibitor homologs include SPI proteins in which amino acids have been deleted (e.g., a truncated version of the protein, such as a peptide), inserted, inverted, substituted and/or derivatized (e.g., by glycosylation, phosphorylation, acetylation, myristoylation, prenylation, palmitoylation, amidation and/or addition of glycerophosphatidyl inositol) such that the homolog includes at least one epitope capable of eliciting an immune response against a flea protein or has at least some serine protease inhibitor activity. For example, when the homolog is administered to an animal as an immunogen, using techniques known to those skilled in the art, the animal will produce an immune response against at least one epitope of a natural flea SPI protein. The ability of a protein to effect an immune response, can be measured using techniques known to those skilled in the art. Techniques to measure serine protease inhibitor activity are also known to those skilled in the art; see, for example, Jiang et al., 1995, *Insect Biochem. Molec. Biol. 25,* 1093-1100.

Flea SPI protein homologs can be the result of natural allelic variation or natural mutation. SPI protein homologs of the present invention can also be produced using techniques known in the art including, but not limited to, direct modifications to the protein or modifications to the gene encoding the protein using, for example, classic or recombinant nucleic acid techniques to effect random or targeted mutagenesis.

Isolated SPI proteins of the present invention have the further characteristic of being encoded by nucleic acid molecules that hybridize under stringent hybridization conditions to a gene encoding a *Ctenocephalides felis* SPI protein (i.e., a *C. felis* SPI gene). As used herein, stringent hybridization conditions refer to standard hybridization conditions under which nucleic acid molecules, including oligonucleotides, are used to identify similar nucleic acid molecules. Such standard conditions are disclosed, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, 1989; Sambrook et al., *ibid.*, is incorporated by reference herein in its entirety. Stringent hybridization conditions typically permit isolation of nucleic acid

molecules having at least about 70% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction. Formulae to calculate the appropriate hybridization and wash conditions to achieve hybridization permitting 30% or less mismatch of nucleotides are disclosed, for example, in Meinkoth et al., 1984, *Anal. Biochem.* 138, 267-284; Meinkoth et al., *ibid.*, is incorporated by reference herein in its entirety.

As used herein, a *C. felis* SPI gene includes all nucleic acid sequences related to a natural *C. felis* SPI gene such as regulatory regions that control production of the *C. felis* SPI protein encoded by that gene (such as, but not limited to, transcription, translation or post-translation control regions) as well as the coding region itself. In one embodiment, a *C. felis* SPI gene of the present invention includes the nucleic acid sequence SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:3, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69 and/or SEQ ID NO:71. Nucleic acid sequence SEQ ID NO:1 represents the deduced sequence of the coding strand of a complementary DNA (cDNA) nucleic acid molecule denoted herein as $nfSPI1_{1584}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:1 (represented herein by SEQ ID NO:3) refers to the nucleic acid sequence of the strand complementary to the strand having SEQ ID NO:1, which can easily be determined by those skilled in the art. Likewise, a nucleic acid sequence complement of any nucleic acid sequence of the present invention refers to the nucleic acid sequence of the nucleic acid strand that is complementary to (i.e., can form a complete double helix with) the strand for which the sequence is cited.

Nucleic acid sequence SEQ ID NO:7 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI2_{1358}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:7 is represented herein by SEQ ID NO:9.

Nucleic acid sequence SEQ ID NO:13 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI3_{1838}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:13 is represented herein by SEQ ID NO:15.

Nucleic acid sequence SEQ ID NO:19 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI4_{1414}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:19 is represented herein by SEQ ID NO:21.

Nucleic acid sequence SEQ ID NO:25 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI5_{1492}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:25 is represented herein by SEQ ID NO:27.

Nucleic acid sequence SEQ ID NO:31 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI6_{1454}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:31 is represented herein by SEQ ID NO:33.

Nucleic acid sequence SEQ ID NO:45 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI7_{549}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:45 is represented herein by SEQ ID NO:47.

Nucleic acid sequence SEQ ID NO:48 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI8_{549}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:48 is represented herein by SEQ ID NO:50.

Nucleic acid sequence SEQ ID NO:51 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI9_{581}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:51 is represented herein by SEQ ID NO:53.

Nucleic acid sequence SEQ ID NO:54 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI10_{654}$, the

production of which is disclosed in the Examples. The complement of SEQ ID NO:54 is represented herein by SEQ ID NO:56.

Nucleic acid sequence SEQ ID NO:57 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI11_{670}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:57 is represented herein by SEQ ID NO:59.

Nucleic acid sequence SEQ ID NO:60 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI12_{706}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:60 is represented herein by SEQ ID NO:62.

Nucleic acid sequence SEQ ID NO:63 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI13_{623}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:63 is represented herein by SEQ ID NO:65.

Nucleic acid sequence SEQ ID NO:66 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI14_{731}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:66 is represented herein by SEQ ID NO:68.

Nucleic acid sequence SEQ ID NO:69 represents the deduced sequence of the coding strand of a cDNA nucleic acid molecule denoted herein as $nfSPI15_{685}$, the production of which is disclosed in the Examples. The complement of SEQ ID NO:69 is represented herein by SEQ ID NO:71.

It should be noted that since nucleic acid sequencing technology is not entirely error-free, SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:31, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:54, SEQ ID NO:57, SEQ ID NO:60, SEQ ID NO:63, SEQ ID NO:66 and SEQ ID NO:69, and complements thereof (as well as other nucleic acid and protein sequences presented herein), at best, represent apparent nucleic acid sequences of certain nucleic acid molecules encoding *C. felis* SPI proteins of the present invention.

In another embodiment, a *C. felis* SPI gene can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4,

SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90. An allelic variant of a *C. felis* SPI gene is a gene that occurs at essentially the same locus (or loci) in the genome as the gene including SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, but which, due to natural variations caused by, for example, mutation or recombination, has a similar but not identical sequence. Allelic variants typically encode proteins having similar activity to that of the protein encoded by the gene to which they are being compared. Allelic variants can also comprise alterations in the 5' or 3' untranslated regions of the gene (e.g., in regulatory control regions). Allelic variants are well known to those skilled in the art and would be expected to be found within a given flea since the genome is diploid and/or among a group of two or more fleas.

The minimal size of a SPI protein homolog of the present invention is a size sufficient to be encoded by a nucleic acid molecule capable of forming a stable hybrid

(i.e., hybridize under stringent hybridization conditions) with the complementary sequence of a nucleic acid molecule encoding the corresponding natural protein. As such, the size of the nucleic acid molecule encoding such a protein homolog is dependent on nucleic acid composition and percent homology between the nucleic acid molecule and complementary sequence. It should also be noted that the extent of homology required to form a stable hybrid can vary depending on whether the homologous sequences are interspersed throughout the nucleic acid molecules or are clustered (i.e., localized) in distinct regions on the nucleic acid molecules. The minimal size of such nucleic acid molecules is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecules are GC-rich and at least about 15 to about 17 bases in length if they are AT-rich. As such, the minimal size of a nucleic acid molecule used to encode a SPI protein homolog of the present invention is from about 12 to about 18 nucleotides in length. Thus, the minimal size of a SPI protein homolog of the present invention is from about 4 to about 6 amino acids in length. There is no limit, other than a practical limit, on the maximal size of such a nucleic acid molecule in that the nucleic acid molecule can include a portion of a gene, an entire gene, multiple genes, or portions thereof. The preferred size of a protein encoded by a nucleic acid molecule of the present invention depends on whether a full-length, fusion, multivalent, or functional portion of such a protein is desired.

Suitable fleas from which to isolate SPI proteins of the present invention (including isolation of the natural protein or production of the protein by recombinant or synthetic techniques) include *Ctenocephalides*, *Ceratophyllus*, *Diamanus*, *Echidnophaga*, *Nosopsyllus*, *Pulex*, *Tunga*, *Oropsylla*, *Orchopeus* and *Xenopsylla*. More preferred fleas from which to isolate SPI proteins include *Ctenocephalides felis*, *Ctenocephalides canis*, *Ceratophyllus pulicidae*, *Pulex irritans*, *Oropsylla (Thrassis) bacchi*, *Oropsylla (Diamanus) montana*, *Orchopeus howardi*, *Xenopsylla cheopis* and *Pulex simulans*, with *C. felis* being even more preferred.

Suitable flea tissues from which to isolate a SPI protein of the present invention includes tissues from unfed fleas or tissue from fleas that recently consumed a blood meal (i.e., blood-fed fleas). Such flea tissues are referred to herein as, respectively, unfed flea tissues and fed flea tissues. Preferred flea tissues from which to obtain a SPI

protein of the present invention includes unfed or fed pre-pupal larval, 1st instar larval, 2nd instar larval, 3rd instar larval, and/or adult flea tissues. More preferred flea tissue includes prepupal larval tissue. A SPI of the present invention is also preferably obtained from hemolymph.

A preferred flea SPI protein of the present invention is a compound that when administered to an animal in an effective manner, is capable of protecting that animal from a hematophagous ectoparasite infestation. In accordance with the present invention, the ability of a SPI protein of the present invention to protect an animal from a hematophagous ectoparasite infestation refers to the ability of that protein to, for example, treat, ameliorate and/or prevent infestation caused by a hematophagous ectoparasite. In particular, the phrase "to protect an animal from hematophagous ectoparasite infestation" refers to reducing the potential for hematophagous ectoparasite population expansion on and around the animal (i.e., reducing the hematophagous ectoparasite burden). Preferably, the hematophagous ectoparasite population size is decreased, optimally to an extent that the animal is no longer bothered by hematophagous ectoparasites. A host animal, as used herein, is an animal from which hematophagous ectoparasites can feed by attaching to and feeding through the skin of the animal. Hematophagous ectoparasites, and other ectoparasites, can live on a host animal for an extended period of time or can attach temporarily to an animal in order to feed. At any given time, a certain percentage of a hematophagous ectoparasite population can be on a host animal whereas the remainder can be in the environment of the animal. Such an environment can include not only adult hematophagous ectoparasites, but also hematophagous ectoparasite eggs and/or hematophagous ectoparasite larvae. The environment can be of any size such that hematophagous ectoparasite in the environment are able to jump onto and off of a host animal. For example, the environment of an animal can include plants, such as crops, from which hematophagous ectoparasites infest an animal. As such, it is desirable not only to reduce the hematophagous ectoparasite burden on an animal per se, but also to reduce the hematophagous ectoparasite burden in the environment of the animal. In one embodiment, a SPI protein of the present invention can elicit an immune response

(including a humoral and/or cellular immune response) against a hematophagous ectoparasite.

Suitable hematophagous ectoparasites to target include any hematophagous ectoparasite that is essentially incapable of infesting an animal administered a SPI protein of the present invention. As such, a hematophagous ectoparasite to target includes any hematophagous ectoparasite that produces a protein having one or more epitopes that can be targeted by a humoral and/or cellular immune response against a SPI protein of the present invention, that can be targeted by a compound that otherwise inhibits SPI activity, and/or that can be targeted by a SPI protein (e.g., a peptide) or mimetope of a SPI protein of the present invention in such a manner as to inhibit serine protease activity, thereby resulting in the decreased ability of the hematophagous ectoparasite to infest an animal. Preferred hematophagous ectoparasite to target include insects and acarines. A SPI protein of the present invention preferably protects an animal from infestation by hematophagous ectoparasites including, but are not limited to, agricultural pests, stored product pests, forest pests, structural pests or animal health pests. Suitable agricultural pests of the present invention include, but are not limited to, Colorado potato beetles, corn earworms, fleahoppers, weevils, pink boll worms, cotton aphids, beet armyworms, lygus bugs, hessian flies, sod webworms, whites grubs, diamond back moths, white flies, planthoppers, leafhoppers, mealy bugs, mormon crickets and mole crickets. Suitable stored product pests of the present invention include, but are not limited to, dermestids, anobeids, saw toothed grain beetles, indian mealmoths, flour beetles, long-horn wood boring beetles and metallic wood boring beetles. Suitable forest pests of the present invention include, but are not limited to, southern pine bark beetles, gypsy moths, elm beetles, ambrosia bettles, bag worms, tent worms and tussock moths. Suitable structural pests of the present invention include, but are not limited to, bess beetles, termites, fire ants, carpenter ants, wasps, hornets, cockroaches, silverfish, *Musca domestica* and *Musca autumnalis*. Suitable animal health pests of the present invention include, but are not limited to, fleas, ticks, mosquitoes, black flies, lice, true bugs, sand flies, *Psychodidae*, tsetse flies, sheep blow flies, cattle grub, mites, horn flies, heel flies, deer flies, *Culicoides* and warble flies. A SPI protein of the present invention more preferably protects an animal from infestation by

hematophagous ectoparasites including fleas, midges, mosquitos, sand flies, black flies, horse flies, snipe flies, louse flies, horn flies, deer flies, tsetse flies, buffalo flies, blow flies, stable flies, myiasis-causing flies, biting gnats, lice, mites, bee, wasps, ants, true bugs and ticks, even more preferably fleas and ticks, and even more preferably fleas. Preferred fleas from which to protect an animal from flea infestation include those disclosed herein for the isolation of a SPI of the present invention.

The present invention also includes mimetopes of SPI proteins of the present invention. As used herein, a mimetope of a SPI protein of the present invention refers to any compound that is able to mimic the activity of such a SPI protein (e.g., ability to elicit an immune response against a SPI protein of the present invention and/or ability to inhibit serine protease activity), often because the mimetope has a structure that mimics the SPI protein. It is to be noted, however, that the mimetope need not have a structure similar to an SPI protein as long as the mimetope functionally mimics the protein. Mimetopes can be, but are not limited to: peptides that have been modified to decrease their susceptibility to degradation; anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous immunogenic portions of an isolated protein (e.g., carbohydrate structures); synthetic or natural organic or inorganic molecules, including nucleic acids; and/or any other peptidomimetic compounds. Mimetopes of the present invention can be designed using computer-generated structures of SPI proteins of the present invention. Mimetopes can also be obtained by generating random samples of molecules, such as oligonucleotides, peptides or other organic molecules, and screening such samples by affinity chromatography techniques using the corresponding binding partner, (e.g., a flea serine protease or anti-flea serine protease inhibitor antibody). A preferred mimetope is a peptidomimetic compound that is structurally and/or functionally similar to a SPI protein of the present invention, particularly to the active site of the SPI protein.

One embodiment of a flea SPI protein of the present invention is a fusion protein that includes a flea SPI protein-containing domain attached to one or more fusion segments. Suitable fusion segments for use with the present invention include, but are not limited to, segments that can: enhance a protein's stability; act as an immunopotentiator to enhance an immune response against a SPI protein; and/or assist

purification of a SPI protein (e.g., by affinity chromatography). A suitable fusion segment can be a domain of any size that has the desired function (e.g., imparts increased stability, imparts increased immunogenicity to a protein, and/or simplifies purification of a protein). Fusion segments can be joined to amino and/or carboxyl termini of the SPI-containing domain of the protein and can be susceptible to cleavage in order to enable straight-forward recovery of a SPI protein. Fusion proteins are preferably produced by culturing a recombinant cell transformed with a fusion nucleic acid molecule that encodes a protein including the fusion segment attached to either the carboxyl and/or amino terminal end of a SPI-containing domain. Preferred fusion segments include a metal binding domain (e.g., a poly-histidine segment); an immunoglobulin binding domain (e.g., Protein A; Protein G; T cell; B cell; Fc receptor or complement protein antibody-binding domains); a sugar binding domain (e.g., a maltose binding domain); and/or a "tag" domain (e.g., at least a portion of β-galactosidase, a strep tag peptide, other domains that can be purified using compounds that bind to the domain, such as monoclonal antibodies). More preferred fusion segments include metal binding domains, such as a poly-histidine segment; a maltose binding domain; a strep tag peptide, such as that available from Biometra in Tampa, FL; and an S10 peptide. Examples of particularly preferred fusion proteins of the present invention include PHis-PfSPI2_{376}, PHis-PfSPI3_{390}, PHis-PfSPI4_{376}, PHis-PfSPI6_{376}, PHis-PfSPIC4:V7, PHis-PfSPIC4:V8, PHis-PfSPIC4:V9, PHis-PfSPIC4:V10, PHis-PfSPIC4:V12, PHis-PfSPIC4:V13 and PHis-PfSPIC4:V15, production of which are disclosed herein.

In another embodiment, a flea SPI protein of the present invention also includes at least one additional protein segment that is capable of protecting an animal from hematophagous ectoparasite infestations. Such a multivalent protective protein can be produced by culturing a cell transformed with a nucleic acid molecule comprising two or more nucleic acid domains joined together in such a manner that the resulting nucleic acid molecule is expressed as a multivalent protective compound containing at least two protective compounds, or portions thereof, capable of protecting an animal from hematophagous ectoparasite infestation by, for example, targeting two different flea proteins.

Examples of multivalent protective compounds include, but are not limited to, a SPI protein of the present invention attached to one or more compounds protective against one or more flea compounds. Preferred second compounds are proteinaceous compounds that effect active immunization (e.g., antigen vaccines), passive immunization (e.g., antibodies), or that otherwise inhibit a hematophagous ectoparasite activity that when inhibited can reduce hematophagous ectoparasite burden on and around an animal. Examples of second compounds include a compound that inhibits binding between a flea protein and its ligand (e.g., a compound that inhibits flea ATPase activity or a compound that inhibits binding of a peptide or steroid hormone to its receptor), a compound that inhibits hormone (including peptide or steroid hormone) synthesis, a compound that inhibits vitellogenesis (including production of vitellin and/or transport and maturation thereof into a major egg yolk protein), a compound that inhibits fat body function, a compound that inhibits muscle action, a compound that inhibits the nervous system, a compound that inhibits the immune system and/or a compound that inhibits flea feeding. Particular examples of second compounds include, but are not limited to, serine proteases, cysteine proteases, aminopeptidases, calreticulins and esterases, as well as antibodies and inhibitors of such proteins. In one embodiment, a flea SPI protein of the present invention is attached to one or more additional compounds protective against hematophagous ectoparasite infestation. In another embodiment, one or more protective compounds, such as those listed above, can be included in a multivalent vaccine comprising a flea SPI protein of the present invention and one or more other protective molecules as separate compounds.

A preferred flea SPI protein of the present invention is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with at least one of the following nucleic acid molecules: $nfSPI1_{1584}$, $nfSPI1_{1191}$, $nfSPI1_{376}$, $nfSPI2_{1358}$, $nfSPI2_{1197}$, $nfSPI2_{376}$, $nfSPI3_{1838}$, $nfSPI3_{1260}$, $nfSPI3_{391}$, $nfSPI4_{1414}$, $nfSPI4_{1179}$, $nfSPI4_{376}$, $nfSPI5_{1492}$, $nfSPI5_{1194}$, $nfSPI5_{376}$, $nfSPI6_{1454}$, $nfSPI6_{1191}$, $nfSPI6_{376}$, $nfSPI7_{549}$, $nfSPI8_{549}$, $nfSPI9_{581}$, $nfSPI10_{654}$, $nfSPI11_{670}$, $nfSPI12_{706}$, $nfSPI13_{623}$, $nfSPI14_{731}$, $nfSPI15_{685}$, $nfSPI3_{1222}$, $nfSPI6_{1155}$, $nfSPI2_{1065}$ and $nfSPI4_{1070}$. A further preferred isolated protein is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:3,

SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:21, SEQ ID NO:27, and SEQ ID NO:33, SEQ ID NO:47, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:56, SEQ ID NO:59, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:68 and SEQ ID NO:71.

Translation of SEQ ID NO:1 suggests that nucleic acid molecule $nfSPI1_{1584}$ encodes a full-length flea protein of about 397 amino acids, referred to herein as $PfSPI1_{397}$, represented by SEQ ID NO:2, assuming an open reading frame having an initiation (start) codon spanning from about nucleotide 136 through about nucleotide 138 of SEQ ID NO:1 and a termination (stop) codon spanning from about nucleotide 1327 through about nucleotide 1329 of SEQ ID NO:1. The coding region encoding $PfSPI1_{397}$ is represented by nucleic acid molecule $nfSPI1_{1191}$, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:4 and a complementary strand with the nucleic acid sequence represented by SEQ ID NO:5. The deduced amino acid sequence SEQ ID NO:2 suggests a protein having a molecular weight of about 44.4 kilodaltons (kD) and an estimated pI of about 4.97. Analysis of SEQ ID NO:2 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 21. The proposed mature protein, denoted herein as $PfSPI1_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:6. The amino acid sequence of flea $PfSPI1_{376}$ (i.e. SEQ ID NO:6) predicts that $PfSPI1_{376}$ has an estimated molecular weight of about 42.1 kD, an estimated pI of about 4.90, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

Comparison of amino acid sequence SEQ ID NO:2 (i.e., the amino acid sequence of $PfSPI1_{397}$) with amino acid sequences reported in GenBank indicates that SEQ ID NO:2 showed the most homology, i.e., about 36% identity, with GenBank accession number 1378131, a serpin protein from *Manduca sexta*.

Translation of SEQ ID NO:7 suggests that nucleic acid molecule $nfSPI2_{1358}$ encodes a non-full-length flea SPI protein of about 399 amino acids, referred to herein as $PfSPI2_{399}$, represented by SEQ ID NO:8, assuming an open reading frame having a first in-frame codon spanning from about nucleotide 2 through about nucleotide 4 of SEQ ID NO:7 and a termination codon spanning from about nucleotide 1199 through about nucleotide 1201 of SEQ ID NO:7. The coding region encoding $PfSPI2_{399}$ is represented

by nucleic acid molecule $nfSPI2_{1197}$, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:10 and a complementary strand with the nucleic acid sequence represented by SEQ ID NO:11. Analysis of SEQ ID NO:8 suggests the presence of a partial signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 23. The proposed mature protein, denoted herein as $PfSPI2_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:12. The amino acid sequence of flea $PfSPI1_{376}$ (i.e. SEQ ID NO:12) predicts that $PfSPI2_{376}$ has an estimated molecular weight of about 42.1 kD, an estimated pI of about 4.87, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

Comparison of amino acid sequence SEQ ID NO:8 (i.e., the amino acid sequence of $PfSPI2_{399}$) with amino acid sequences reported in GenBank indicates that SEQ ID NO:8, showed the most homology, i.e., about 36% identity, with GenBank accession number 1345616, a serpin protein from *Homo sapiens*.

Translation of SEQ ID NO:13 suggests that nucleic acid molecule $nfSPI3_{1838}$ encodes a full-length flea SPI protein of about 420 amino acids, referred to herein as $PfSPI3_{420}$, represented by SEQ ID NO:14, assuming an open reading frame having an initiation codon spanning from about nucleotide 306 through about nucleotide 308 of SEQ ID NO:13 and a termination codon spanning from about nucleotide 1566 through about nucleotide 1568 of SEQ ID NO:13. The coding region encoding $PfSPI3_{420}$ is represented by nucleic acid molecule $nfSPI3_{1260}$, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:16 and a complementary strand with the nucleic acid sequence represented by SEQ ID NO:17. The deduced amino acid sequence SEQ ID NO:14 suggests a protein having a molecular weight of about 47.1 kilodaltons (kD) and an estimated pI of about 4.72. Analysis of SEQ ID NO:14 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 30. The proposed mature protein, denoted herein as $PfSPI3_{390}$, contains about 390 amino acids which is represented herein as SEQ ID NO:18. The amino acid sequence of flea $PfSPI3_{390}$ (i.e. SEQ ID NO:18) predicts that $PfSPI3_{390}$ has an estimated molecular weight of about 43.7 kD, an estimated pI of about 4.63, and two predicted asparagine-linked glycosylation sites extending from about

amino acid 252 to about amino acid 254 and from about amino acid 369 to about amino acid 371.

Comparison of amino acid sequence SEQ ID NO:14 (i.e., the amino acid sequence of $PfSPI3_{420}$) with amino acid sequences reported in GenBank indicates that SEQ ID NO:14, showed the most homology, i.e., about 35% identity, with GenBank accession number 1345616, a serpin protein from *Homo sapiens*.

Translation of SEQ ID NO:19 suggests that nucleic acid molecule $nfSPI4_{1414}$ encodes a non-full-length flea SPI protein of about 393 amino acids, referred to herein as $PfSPI4_{393}$, represented by SEQ ID NO:20, assuming an open reading frame having a first in-frame codon spanning from about nucleotide 2 through about nucleotide 4 of SEQ ID NO:19 and a termination codon spanning from about nucleotide 1181 through about nucleotide 1183 of SEQ ID NO:19. The coding region encoding $PfSPI4_{393}$, is represented by nucleic acid molecule $nfSPI4_{1179}$, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:22 and a complementary strand with the nucleic acid sequence represented by SEQ ID NO:23. Analysis of SEQ ID NO:20 suggests the presence of a partial signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 17. The proposed mature protein, denoted herein as $PfSPI4_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:24. The amino acid sequence of flea $PfSPI4_{376}$ (i.e. SEQ ID NO:24) predicts that $PfSPI4_{376}$ has an estimated molecular weight of about 42.2 kD, an estimated pI of about 5.31, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

Comparison of amino acid sequence SEQ ID NO:20 (i.e., the amino acid sequence of $PfSPI4_{393}$) with amino acid sequences reported in GenBank indicates that SEQ ID NO:20, showed the most homology, i.e., about 38% identity, with GenBank accession number 1345616, a serpin protein from *Homo sapiens*.

Translation of SEQ ID NO:25 suggests that nucleic acid molecule $nfSPI5_{1492}$ encodes a non-full-length flea SPI protein of about 398 amino acids, referred to herein as $PfSPI5_{398}$, represented by SEQ ID NO:26, assuming an open reading frame having a first in-frame codon spanning from about nucleotide 3 through about nucleotide 5 of SEQ ID NO:25 and a termination codon spanning from about nucleotide 1197 through about

nucleotide 1199 of SEQ ID NO:25. The coding region encoding $PfSPI5_{398}$, is represented by nucleic acid molecule $nfSPI5_{1194}$, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:28 and a complementary strand with the nucleic acid sequence represented by SEQ ID NO:29. Analysis of SEQ ID NO:26 suggests the presence of a partial signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 22. The proposed mature protein, denoted herein as $PfSPI5_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:30. The amino acid sequence of flea $PfSPI5_{376}$ (i.e. SEQ ID NO:30) predicts that $PfSPI5_{376}$ has an estimated molecular weight of about 42.3 kD, an estimated pI of about 5.31 and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

Comparison of amino acid sequence SEQ ID NO:26 (i.e., the amino acid sequence of $PfSPI5_{398}$) with amino acid sequences reported in GenBank indicates that SEQ ID NO:26 showed the most homology, i.e., about 38% identity with GenBank accession number 1345616, a serpin protein from *Homo sapiens*.

Translation of SEQ ID NO:31 suggests that nucleic acid molecule $nfSPI6_{1454}$ encodes a full-length flea SPI protein of about 397 amino acids, referred to herein as $PfSPI6_{397}$, represented by SEQ ID NO:32, assuming an open reading frame having an initiation codon spanning from about nucleotide 20 through about nucleotide 22 of SEQ ID NO:31 and a termination codon spanning from about nucleotide 1211 through about nucleotide 1213 of SEQ ID NO:31. The coding region encoding $PfSPI6_{397}$ is represented by nucleic acid molecule $nfSPI6_{1191}$, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:34 and a complementary strand with the nucleic acid sequence represented by SEQ ID NO:35. The deduced amino acid sequence SEQ ID NO:32 suggests a protein having a molecular weight of about 44.4 kilodaltons (kD) and an estimated pI of about 4.90. Analysis of SEQ ID NO:32 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 21. The proposed mature protein, denoted herein as $PfSPI6_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:36. The amino acid sequence of flea $PfSPI6_{376}$ (i.e. SEQ ID NO:36) predicts that $PfSPI6_{376}$ has an estimated molecular weight of about 42.1 kD, an estimated pI of about 4.84, and a

predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

Comparison of amino acid sequence SEQ ID NO:32 (i.e., the amino acid sequence of $PfSPI6_{397}$) with amino acid sequences reported in GenBank indicates that SEQ ID NO:32 showed the most homology, i.e., about 36% identity with GenBank accession number 1378131, a serpin protein from *Manduca sexta*.

Translation of SEQ ID NO:45 suggests that nucleic acid molecule $nfSPI7_{549}$ encodes a portion of a serine protease inhibitor protein of about 134 amino acids, referred to herein as $PfSPI7_{134}$, having amino acid sequence SEQ ID NO:46, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:45 and the last codon spans from nucleotide 402 through nucleotide 404 of SEQ ID NO:45. The complement of SEQ ID NO:45 is represented herein by SEQ ID NO:47.

Comparison of amino acid sequence SEQ ID NO:46 (i.e., the amino acid sequence of $PfSPI7_{134}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:46, showed the most homology, i.e., about 34% identity, between SEQ ID NO:46 and *mus musculus* antithrombin III precursor protein.

Translation of SEQ ID NO:48 suggests that nucleic acid molecule $nfSPI8_{549}$ encodes a serine protease inhibitor variable domain protein of about 149 amino acids, referred to herein as $PfSPI8_{149}$, having amino acid sequence SEQ ID NO:49, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:48 and the last codon spans from nucleotide 447 through nucleotide 449 of SEQ ID NO:48. The complement of SEQ ID NO:48 is represented herein by SEQ ID NO:50.

Comparison of amino acid sequence SEQ ID NO:49 (i.e., the amino acid sequence of $PfSPI8_{149}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:49, showed the most homology, i.e., about 36% identity, between SEQ ID NO:49 and human bomapin protein.

Translation of SEQ ID NO:51 suggests that nucleic acid molecule $nfSPI9_{581}$ encodes a serine protease inhibitor variable domain protein of about 136 amino acids, referred to herein as $PfSPI9_{136}$, having amino acid sequence SEQ ID NO:52, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:51 and the

last codon spans from nucleotide 408 through nucleotide 410 of SEQ ID NO:51. The complement of SEQ ID NO:51 is represented herein by SEQ ID NO:53.

Comparison of amino acid sequence SEQ ID NO:52 (i.e., the amino acid sequence of $PfSPI9_{136}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:52, showed the most homology, i.e., about 45% identity, between SEQ ID NO:52 and *Bombyx mori* anti-trypsin precusor protein.

Translation of SEQ ID NO:54 suggests that nucleic acid molecule $nfSPI10_{654}$ encodes a serine protease inhibitor variable domain protein of about 118 amino acids, referred to herein as $PfSPI10_{118}$, having amino acid sequence SEQ ID NO:55, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:54 and the last codon spans from nucleotide 354 through nucleotide 356 of SEQ ID NO:54. The complement of SEQ ID NO:54 is represented herein by SEQ ID NO:56.

Comparison of amino acid sequence SEQ ID NO:55 (i.e., the amino acid sequence of $PfSPI10_{118}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:55, showed the most homology, i.e., about 38% identity, between SEQ ID NO:55 and *Manduca sexta* alaserpin precursor protein.

Translation of SEQ ID NO:57 suggests that nucleic acid molecule $nfSPI11_{670}$ encodes a serine protease inhibitor variable domain protein of about 125 amino acids, referred to herein as $PfSPI11_{125}$, having amino acid sequence SEQ ID NO:58, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:57 and the last codon spans from nucleotide 375 through nucleotide 377 of SEQ ID NO:57. The complement of SEQ ID NO:57 is represented herein by SEQ ID NO:59.

Comparison of amino acid sequence SEQ ID NO:58 (i.e., the amino acid sequence of $PfSPI11_{125}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:58, showed the most homology, i.e., about 43% identity, between SEQ ID NO:58 and *Manduca sexta* alaserpin precursor protein.

Translation of SEQ ID NO:60 suggests that nucleic acid molecule $nfSPI12_{706}$ encodes a serine protease inhibitor variable domain protein of about 136 amino acids, referred to herein as $PfSPI12_{136}$, having amino acid sequence SEQ ID NO:61, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:60 and the

last codon spans from nucleotide 408 through nucleotide 410 of SEQ ID NO:60. The complement of SEQ ID NO:60 is represented herein by SEQ ID NO:62.

Comparison of amino acid sequence SEQ ID NO:61 (i.e., the amino acid sequence of $PfSPI12_{136}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:61, showed the most homology, i.e., about 45% identity, between SEQ ID NO:61 and *Manduca sexta* alaserpin precursor protein protein.

Translation of SEQ ID NO:63 suggests that nucleic acid molecule $nfSPI13_{623}$ encodes a serine protease inhibitor variable domain protein of about 122 amino acids, referred to herein as $PfSPI13_{122}$, having amino acid sequence SEQ ID NO:64, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:63 and the last codon spans from nucleotide 366 through nucleotide 368 of SEQ ID NO:63. The complement of SEQ ID NO:63 is represented herein by SEQ ID NO:65.

Comparison of amino acid sequence SEQ ID NO:64 (i.e., the amino acid sequence of $PfSPI13_{122}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:64, showed the most homology, i.e., about 39% identity, between SEQ ID NO:64 and human leukocyte esterase inhibitor protein.

Translation of SEQ ID NO:66 suggests that nucleic acid molecule $nfSPI14_{731}$ encodes a serine protease inhibitor variable domain protein of about 137 amino acids, referred to herein as $PfSPI14_{137}$, having amino acid sequence SEQ ID NO:67, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:66 and the last codon spans from nucleotide 411 through nucleotide 413 of SEQ ID NO:66. The complement of SEQ ID NO:66 is represented herein by SEQ ID NO:68.

Comparison of amino acid sequence SEQ ID NO:67 (i.e., the amino acid sequence of $PfSPI14_{137}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:67, showed the most homology, i.e., about 40% identity, between SEQ ID NO:67 and *Equus callabus* esterase inhibitor protein.

Translation of SEQ ID NO:69 suggests that nucleic acid molecule $nfSPI15_{685}$ encodes a serine protease inhibitor variable domain protein of about 135 amino acids, referred to herein as $PfSPI15_{135}$, having amino acid sequence SEQ ID NO:70, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:69 and the

last codon spans from nucleotide 405 through nucleotide 407 of SEQ ID NO:69. The complement of SEQ ID NO:69 is represented herein by SEQ ID NO:71.

Comparison of amino acid sequence SEQ ID NO:70 (i.e., the amino acid sequence of PfSPI15$_{135}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:70, showed the most homology, i.e., about 48% identity, between SEQ ID NO:70 and Bombyx mori antichymotrypsin II protein.

More preferred flea SPI proteins of the present invention include proteins comprising amino acid sequences that are at least about 40%, preferably at least about 50%, more preferably at least about 60%, more preferably at least about 70%, more preferably at least about 80%, and even more preferably at least about 90%, identical to amino acid sequence SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89 and/or SEQ ID NO:90.

More preferred flea SPI proteins of the present invention include proteins encoded by a nucleic acid molecule comprising at least a portion of nfSPI1$_{1584}$, nfSPI1$_{1191}$, nfSPI1$_{376}$, nfSPI2$_{1358}$, nfSPI2$_{1197}$, nfSPI2$_{376}$, nfSPI3$_{1838}$, nfSPI3$_{1260}$, nfSPI3$_{391}$, nfSPI4$_{1414}$, nfSPI4$_{1179}$, nfSPI4$_{376}$, nfSPI5$_{1492}$, nfSPI5$_{1194}$, nfSPI5$_{376}$, nfSPI6$_{1454}$, nfSPI6$_{1191}$, nfSPI6$_{376}$, nfSPI7$_{549}$, nfSPI8$_{549}$, nfSPI9$_{581}$, nfSPI10$_{654}$, nfSPI11$_{670}$, nfSPI12$_{706}$, nfSPI13$_{623}$, nfSPI14$_{731}$, nfSPI15$_{685}$, nfSPI3$_{1222}$, nfSPI6$_{1155}$, nfSPI2$_{1065}$, nfSPI4$_{1070}$, nfSPIC4:V7$_{1168}$, nfSPIC4:V8$_{1222}$, nfSPIC4:V9$_{1174}$, nfSPIC4:V10$_{1159}$, nfSPIC4:V12$_{1171}$, nfSPIC4:V13$_{1171}$, and nfSPIC4:V15$_{1179}$, or by an allelic variant of such nucleic acid molecules. Particularly preferred flea SPI proteins are PfSPI1$_{397}$, PfSPI1$_{376}$, PfSPI2$_{399}$, PfSPI2$_{376}$, PfSPI2$_{354}$, PfSPI3$_{406}$, PfSPI3$_{420}$, PfSPI3$_{391}$, PfSPI4$_{393}$, PfSPI4$_{376}$, PfSPI4$_{356}$, PfSPI5$_{398}$, PfSPI5$_{376}$, PfSPI6$_{397}$, PfSPI6$_{376}$, PfSPI6$_{385}$, PfSPI2$_{355}$, PfSPI3$_{406}$, PfSPI4$_{356}$, PfSPI6$_{385}$, PfSPI7$_{134}$, PfSPI8$_{149}$, PfSPI9$_{136}$, PfSPI10$_{118}$, PfSPI11$_{125}$, PfSPI12$_{136}$, PfSPI13$_{122}$, PfSPI14$_{137}$, PfSPI15$_{135}$, PHis-PfSPIC4:V7, PHis-PfSPIC4:V8, PHis-PfSPIC4:V9, PHis-PfSPIC4:V10, PHis-PfSPIC4:V12, PHis-PfSPIC4:V13, PHis-PfSPIC4:V15.

In one embodiment, a preferred SPI protein of the present invention is encoded by at least a portion of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:10,

SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:54, SEQ ID NO:57, SEQ ID NO:60, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81 and/or a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, and, as such, has an amino acid sequence that includes at least a portion of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70 SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, respectively.

Also preferred is a protein encoded by an allelic variant of a nucleic acid molecule comprising at least a portion of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:54, SEQ ID NO:57, SEQ ID NO:60, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, and/or a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90. Particularly preferred SPI proteins of the present invention include SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO: 97, and/or SEQ ID NO:98 (including, but not limited to, the proteins consisting of such sequences, fusion proteins and multivalent proteins) and proteins encoded by allelic variants of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:51, SEQ ID

NO:54, SEQ ID NO:57, SEQ ID NO:60, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, and/or a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90.

Another embodiment of the present invention is an isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a *C. felis* SPI gene. The identifying characteristics of such a gene are heretofore described. A nucleic acid molecule of the present invention can include an isolated natural flea SPI gene or a homolog thereof, the latter of which is described in more detail below. A nucleic acid molecule of the present invention can include one or more regulatory regions, full-length or partial coding regions, or combinations thereof. The minimal size of a nucleic acid molecule of the present invention is the minimal size that can form a stable hybrid with a *C. felis* SPI gene under stringent hybridization conditions.

In accordance with the present invention, an isolated nucleic acid molecule is a nucleic acid molecule that has been removed from its natural milieu (i.e., that has been subject to human manipulation) and can include DNA, RNA, or derivatives of either DNA or RNA. As such, "isolated" does not reflect the extent to which the nucleic acid molecule has been purified. An isolated flea SPI nucleic acid molecule of the present invention can be isolated from its natural source or can be produced using recombinant DNA technology (e.g., polymerase chain reaction (PCR) amplification, cloning) or chemical synthesis. Isolated SPI nucleic acid molecules can include, for example, natural allelic variants and nucleic acid molecules modified by nucleotide insertions, deletions, substitutions, and/or inversions in a manner such that the modifications do not substantially interfere with the nucleic acid molecule's ability to encode a SPI protein of the present invention or to form stable hybrids under stringent conditions with natural gene isolates.

A flea SPI nucleic acid molecule homolog can be produced using a number of methods known to those skilled in the art (see, for example, Sambrook et al., *ibid.*). For example, nucleic acid molecules can be modified using a variety of techniques including, but not limited to, classic mutagenesis and recombinant DNA techniques (e.g., site-directed mutagenesis, chemical treatment, restriction enzyme cleavage,

ligation of nucleic acid fragments and/or PCR amplification), synthesis of oligonucleotide mixtures and ligation of mixture groups to "build" a mixture of nucleic acid molecules and combinations thereof. Nucleic acid molecule homologs can be selected by hybridization with a *C. felis* SPI gene or by screening for function of a protein encoded by the nucleic acid molecule (e.g., ability to elicit an immune response against at least one epitope of a flea SPI protein or has at least some serine protease inhibitor activity).

An isolated nucleic acid molecule of the present invention can include a nucleic acid sequence that encodes at least one flea SPI protein of the present invention, examples of such proteins being disclosed herein. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a flea SPI protein.

A preferred nucleic acid molecule of the present invention, when administered to an animal, is capable of protecting that animal from infestation by a hematophagous ectoparasite. As will be disclosed in more detail below, such a nucleic acid molecule can be, or can encode, an antisense RNA, a molecule capable of triple helix formation, a ribozyme, or other nucleic acid-based drug compound. In additional embodiments, a nucleic acid molecule of the present invention can encode a protective protein (e.g., a SPI protein of the present invention), the nucleic acid molecule being delivered to the animal, for example, by direct injection (i.e, as a naked nucleic acid) or in a vehicle such as a recombinant virus vaccine or a recombinant cell vaccine.

One embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI1_{1584}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:1 and/or SEQ ID NO:3.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI2_{1358}$

and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:7 and/or SEQ ID NO:9.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI3_{1838}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:13 and/or SEQ ID NO:15.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI4_{1414}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:19 and/or SEQ ID NO:21.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI5_{1492}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:25 and/or SEQ ID NO:27.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI6_{1454}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:31 and/or SEQ ID NO:33.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI7_{549}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:45 and/or SEQ ID NO:47.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI8_{549}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:48 and/or SEQ ID NO:50.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI9_{581}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:51 and/or SEQ ID NO:53.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI10_{654}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:54 and/or SEQ ID NO:56.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI11_{670}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:57 and/or SEQ ID NO:59.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI12_{706}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:60 and/or SEQ ID NO:62.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI13_{623}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:63 and/or SEQ ID NO:65.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI14_{731}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:66 and/or SEQ ID NO:68.

Another embodiment of the present invention is a SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with nucleic acid molecule $nfSPI15_{685}$ and preferably with a nucleic acid molecule having nucleic acid sequence SEQ ID NO:69 and/or SEQ ID NO:71.

Comparison of nucleic acid sequence SEQ ID NO:4 (i.e., the nucleic acid sequence of the coding strand of $nfSPI1_{1191}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:4 showed the most homology, i.e., about 55% identity, with accession number L20792, a putative serine proteinase inhibitor (serpin 1, exon 9 copy 2) gene of *Manduca sexta*.

Comparison of nucleic acid sequence SEQ ID NO:10 (i.e., the nucleic acid sequence of the coding strand of $nfSPI2_{1197}$) with nucleic acid sequences reported in

GenBank indicates that SEQ ID NO:10 showed the most homology, i.e., about 43% identity, with accession number L20790, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 1) of *Manduca sexta*.

Comparison of nucleic acid sequence SEQ ID NO:16 (i.e., the nucleic acid sequence of the coding strand of nfSPI3$_{1260}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:16 showed the most homology, i.e., about 52% identity, with accession number L20792, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 2) of *Manduca sexta*.

Comparison of nucleic acid sequence SEQ ID NO:22 (i.e., the nucleic acid sequence of the coding strand of nfSPI4$_{1179}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:22 showed the most homology, i.e., about 55% identity, with accession number L20793, a putative serine proteinase inhibitor gene (serpin 1, exon 9 unknown copy number) of *Manduca sexta*.

Comparison of nucleic acid sequence SEQ ID NO:28 (i.e., the nucleic acid sequence of the coding strand of nfSPI5$_{1194}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:28 showed the most homology, i.e., about 45% identity, with accession number L20790, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 1) of *Manduca sexta*.

Comparison of nucleic acid sequence SEQ ID NO:34 (i.e., the nucleic acid sequence of the coding strand of nfSPI6$_{1191}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:34 showed the most homology, i.e., about 55% identity, with accession number L20792, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 2) of *Manduca sexta*.

Comparison of nucleic acid sequence SEQ ID NO:45 (i.e., the nucleic acid sequence of nfSPI7$_{549}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:45, showed the most homology, i.e., about 38% identity, between SEQ ID NO:45 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:48 (i.e., the nucleic acid sequence of nfSPI8$_{549}$) with nucleic acid sequences reported in GeEmbl indicates that SEQ ID NO:48, showed the most homology, i.e., about 41% identity, between SEQ ID NO:48 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:51 (i.e., the nucleic acid sequence of nfSPI9$_{581}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:51, showed the most homology, i.e., about 52% identity, between SEQ ID NO:51 and *Bombyx mori* anti-trypsin gene.

Comparison of nucleic acid sequence SEQ ID NO:54 (i.e., the nucleic acid sequence of nfSPI10$_{654}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:54, showed the most homology, i.e., about 41% identity, between SEQ ID NO:54 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:57 (i.e., the nucleic acid sequence of nfSPI11$_{670}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:57, showed the most homology, i.e., about 40% identity, between SEQ ID NO:57 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:60 (i.e., the nucleic acid sequence of nfSPI12$_{706}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:60, showed the most homology, i.e., about 38% identity, between SEQ ID NO:60 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:63 (i.e., the nucleic acid sequence of nfSPI13$_{623}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:63, showed the most homology, i.e., about 37% identity, between SEQ ID NO:63 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:66 (i.e., the nucleic acid sequence of nfSPI14$_{731}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:66, showed the most homology, i.e., about 38% identity, between SEQ ID NO:66 and human bomapin gene.

Comparison of nucleic acid sequence SEQ ID NO:69 (i.e., the nucleic acid sequence of nfSPI15$_{685}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:69, showed the most homology, i.e., about 38% identity, between SEQ ID NO:69 and human antithrombin III variant gene.

Preferred flea SPI nucleic acid molecules include nucleic acid molecules having a nucleic acid sequence that is at least about 60%, preferably at least about 70%, more preferably at least about 80%, even more preferably at least about 90% and even more

preferably at least about 95% identical to nucleic acid sequence SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90.

Another preferred nucleic acid molecule of the present invention includes at least a portion of nucleic acid sequence SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, that is capable of hybridizing to a *C. felis* SPI gene of the present invention, as well as allelic variants thereof. A more preferred nucleic acid molecule includes the nucleic acid sequence SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID

NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence including SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, as well as allelic variants thereof. Such nucleic acid molecules can include nucleotides in addition to those included in the SEQ ID NOs, such as, but not limited to, a full-length gene, a full-length coding region, a nucleic acid molecule encoding a fusion protein, or a nucleic acid molecule encoding a multivalent protective compound. Particularly preferred nucleic acid molecules include $nfSPI1_{1584}$, $nfSPI1_{1191}$, $nfSPI1_{376}$, $nfSPI2_{1358}$, $nfSPI2_{1197}$, $nfSPI2_{376}$, $nfSPI3_{1838}$, $nfSPI3_{1260}$, $nfSPI3_{391}$, $nfSPI4_{1414}$, $nfSPI4_{1179}$, $nfSPI4_{376}$, $nfSPI5_{1492}$, $nfSPI5_{1194}$, $nfSPI5_{376}$, $nfSPI6_{1454}$, $nfSPI6_{1191}$, $nfSPI6_{376}$, $nfSPI7_{549}$, $nfSPI8_{549}$, $nfSPI9_{581}$, $nfSPI10_{654}$, $nfSPI11_{670}$, $nfSPI12_{706}$, $nfSPI13_{623}$, $nfSPI14_{731}$, $nfSPI15_{685}$, $nfSPI3_{1222}$, $nfSPI6_{1155}$, $nfSPI2_{1065}$, $nfSPI4_{1070}$, $nfSPIC4{:}V7_{1168}$, $nfSPIC4{:}V8_{1222}$, $nfSPIC4{:}V9_{1174}$, $nfSPIC4{:}V10_{1159}$, $nfSPIC4{:}V12_{1171}$, $nfSPIC4{:}V13_{1171}$, and $nfSPIC4{:}V15_{1179}$.

The present invention also includes a nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO: 97, and SEQ ID NO:98, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

Knowing the nucleic acid sequences of certain flea SPI nucleic acid molecules of the present invention allows one skilled in the art to, for example, (a) make copies of those nucleic acid molecules, (b) obtain nucleic acid molecules including at least a portion of such nucleic acid molecules (e.g., nucleic acid molecules including full-length genes, full-length coding regions, regulatory control sequences, truncated coding regions), and (c) obtain SPI nucleic acid molecules from other hematophagous

ectoparasites. Such nucleic acid molecules can be obtained in a variety of ways including screening appropriate expression libraries with antibodies of the present invention; traditional cloning techniques using oligonucleotide probes of the present invention to screen appropriate libraries or DNA; and PCR amplification of appropriate libraries or DNA using oligonucleotide primers of the present invention. Preferred libraries to screen or from which to amplify nucleic acid molecule include flea hemocyte (i.e., cells found in flea hemolymph), pre-pupal, mixed instar (i.e., a combination of 1st instar larval, 2nd instar larval, 3rd instar larval tissue), or fed or unfed adult cDNA libraries as well as genomic DNA libraries. Similarly, preferred DNA sources to screen or from which to amplify nucleic acid molecules include flea hemocyte, pre-pupal, mixed instar, or fed or unfed adult cDNA and genomic DNA. Techniques to clone and amplify genes are disclosed, for example, in Sambrook et al., *ibid.*

The present invention also includes nucleic acid molecules that are oligonucleotides capable of hybridizing, under stringent hybridization conditions, with complementary regions of other, preferably longer, nucleic acid molecules of the present invention such as those comprising flea SPI genes or other flea SPI nucleic acid molecules. Oligonucleotides of the present invention can be RNA, DNA, or derivatives of either. The minimum size of such oligonucleotides is the size required for formation of a stable hybrid between an oligonucleotide and a complementary sequence on a nucleic acid molecule of the present invention. Minimal size characteristics are disclosed herein. The present invention includes oligonucleotides that can be used as, for example, probes to identify nucleic acid molecules, primers to produce nucleic acid molecules or therapeutic reagents to inhibit SPI protein production or activity (e.g., as antisense-, triplex formation-, ribozyme- and/or RNA drug-based reagents). The present invention also includes the use of such oligonucleotides to protect animals from disease using one or more of such technologies. Appropriate oligonucleotide-containing therapeutic compositions can be administered to an animal using techniques known to those skilled in the art.

One embodiment of the present invention includes a recombinant vector, which includes at least one isolated nucleic acid molecule of the present invention, inserted into any vector capable of delivering the nucleic acid molecule into a host cell. Such a vector

contains heterologous nucleic acid sequences, that is nucleic acid sequences that are not naturally found adjacent to nucleic acid molecules of the present invention and that preferably are derived from a species other than the species from which the nucleic acid molecule(s) are derived. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a virus or a plasmid. Recombinant vectors can be used in the cloning, sequencing, and/or otherwise manipulation of flea SPI nucleic acid molecules of the present invention.

One type of recombinant vector, referred to herein as a recombinant molecule, comprises a nucleic acid molecule of the present invention operatively linked to an expression vector. The phrase operatively linked refers to insertion of a nucleic acid molecule into an expression vector in a manner such that the molecule is able to be expressed when transformed into a host cell. As used herein, an expression vector is a DNA or RNA vector that is capable of transforming a host cell and of effecting expression of a specified nucleic acid molecule. Preferably, the expression vector is also capable of replicating within the host cell. Expression vectors can be either prokaryotic or eukaryotic, and are typically viruses or plasmids. Expression vectors of the present invention include any vectors that function (i.e., direct gene expression) in recombinant cells of the present invention, including in bacterial, fungal, endoparasite, insect, other animal, and plant cells. Preferred expression vectors of the present invention can direct gene expression in bacterial, yeast, insect and mammalian cells and more preferably in the cell types disclosed herein.

In particular, expression vectors of the present invention contain regulatory sequences such as transcription control sequences, translation control sequences, origins of replication, and other regulatory sequences that are compatible with the recombinant cell and that control the expression of nucleic acid molecules of the present invention. In particular, recombinant molecules of the present invention include transcription control sequences. Transcription control sequences are sequences which control the initiation, elongation, and termination of transcription. Particularly important transcription control sequences are those which control transcription initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in at least one of

the recombinant cells of the present invention. A variety of such transcription control sequences are known to those skilled in the art. Preferred transcription control sequences include those which function in bacterial, yeast, insect and mammalian cells, such as, but not limited to, *tac*, *lac*, *trp*, *trc*, oxy-pro, omp/lpp, rrnB, bacteriophage lambda(such as lambda p_L and lambda p_R and fusions that include such promoters), bacteriophage T7, T7*lac*, bacteriophage T3, bacteriophage SP6, bacteriophage SP01, metallothionein, alpha-mating factor, *Pichia* alcohol oxidase, alphavirus subgenomic promoters (such as Sindbis virus subgenomic promoters), antibiotic resistance gene, baculovirus, *Heliothis zea* insect virus, vaccinia virus, herpesvirus, raccoon poxvirus, other poxvirus, adenovirus, cytomegalovirus (such as intermediate early promoters), simian virus 40, retrovirus, actin, retroviral long terminal repeat, Rous sarcoma virus, heat shock, phosphate and nitrate transcription control sequences as well as other sequences capable of controlling gene expression in prokaryotic or eukaryotic cells. Additional suitable transcription control sequences include tissue-specific promoters and enhancers as well as lymphokine-inducible promoters (e.g., promoters inducible by interferons or interleukins). Transcription control sequences of the present invention can also include naturally occurring transcription control sequences naturally associated with fleas, such as, *C. felis*.

Suitable and preferred nucleic acid molecules to include in recombinant vectors of the present invention are as disclosed herein. Preferred nucleic acid molecules to include in recombinant vectors, and particularly in recombinant molecules, include $nfSPI1_{1584}$, $nfSPI1_{1191}$, $nfSPI1_{376}$, $nfSPI2_{1358}$, $nfSPI2_{1197}$, $nfSPI2_{376}$, $nfSPI3_{1838}$, $nfSPI3_{1260}$, $nfSPI3_{391}$, $nfSPI4_{1414}$, $nfSPI4_{1179}$, $nfSPI4_{376}$, $nfSPI5_{1492}$, $nfSPI5_{1194}$, $nfSPI5_{376}$, $nfSPI6_{1454}$, $nfSPI6_{1191}$, $nfSPI6_{376}$, $nfSPI7_{549}$, $nfSPI8_{549}$, $nfSPI9_{581}$, $nfSPI10_{654}$, $nfSPI11_{670}$, $nfSPI12_{706}$, $nfSPI13_{623}$, $nfSPI14_{731}$, $nfSPI15_{685}$, $nfSPI3_{1222}$, $nfSPI6_{1155}$, $nfSPI2_{1065}$, $nfSPI4_{1070}$, $nfSPIC4{:}V7_{1168}$, $nfSPIC4{:}V8_{1222}$, $nfSPIC4{:}V9_{1174}$, $nfSPIC4{:}V10_{1159}$, $nfSPIC4{:}V12_{1171}$, $nfSPIC4{:}V13_{1171}$, and $nfSPIC4{:}V15_{1179}$. Particularly preferred recombinant molecules of the present invention include $p\lambda P_R$-$nfSPI2_{1139}$, $p\lambda P_R$-$nfSPI3_{1179}$, $p\lambda P_R$-$nfSPI4_{1140}$, $p\lambda P_R$-$nfSPI5_{1492}$, $p\lambda P_R$-$nfSPI6_{1136}$,$p\lambda P_R$-$nfSPIC4{:}V7_{1168}$, $p\lambda P_R$-$nfSPIC4{:}V8_{1222}$, $p\lambda P_R$-$nfSPIC4{:}V9_{1174}$, $p\lambda P_R$-n $nfSPIC4{:}V10_{1159}$, $p\lambda P_R$-$nfSPIC4{:}V12_{1171}$, $p\lambda P_R$-$nfSPIC4{:}V13_{1171}$,

pλP$_R$-nfSPIC4:V15$_{1179}$, pVL-nfSPI3$_{1222}$, pVL-nfSPI6$_{1155}$, pAcG-nfSPI2$_{1065}$ and pAcG-nfSPI4$_{1070}$, the production of which are described in the Examples section.

Recombinant molecules of the present invention may also (a) contain secretory signals (i.e., signal segment nucleic acid sequences) to enable an expressed flea protein of the present invention to be secreted from the cell that produces the protein and/or (b) contain fusion sequences which lead to the expression of nucleic acid molecules of the present invention as fusion proteins. Examples of suitable signal segments include any signal segment capable of directing the secretion of a protein of the present invention. Preferred signal segments include, but are not limited to, tissue plasminogen activator (t-PA), interferon, interleukin, growth hormone, histocompatibility and viral envelope glycoprotein signal segments, as well as natural signal segments. Suitable fusion segments encoded by fusion segment nucleic acids are disclosed herein. In addition, a nucleic acid molecule of the present invention can be joined to a fusion segment that directs the encoded protein to the proteosome, such as a ubiquitin fusion segment. Recombinant molecules may also include intervening and/or untranslated sequences surrounding and/or within the nucleic acid sequences of nucleic acid molecules of the present invention.

Another embodiment of the present invention includes a recombinant cell comprising a host cell transformed with one or more recombinant molecules of the present invention. Transformation of a nucleic acid molecule into a cell can be accomplished by any method by which a nucleic acid molecule can be inserted into the cell. Transformation techniques include, but are not limited to, transfection, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. A recombinant cell may remain unicellular or may grow into a tissue, organ or a multicellular organism. Transformed nucleic acid molecules of the present invention can remain extrachromosomal or can integrate into one or more sites within a chromosome of the transformed (i.e., recombinant) cell in such a manner that their ability to be expressed is retained. Preferred nucleic acid molecules with which to transform a cell include flea SPI nucleic acid molecules disclosed herein. Particularly preferred nucleic acid molecules with which to transform a cell include nfSPI1$_{1584}$, nfSPI1$_{1191}$, nfSPI1$_{376}$, nfSPI2$_{1358}$, nfSPI2$_{1197}$, nfSPI2$_{376}$, nfSPI3$_{1838}$, nfSPI3$_{1260}$, nfSPI3$_{391}$,

nfSPI4$_{1414}$, nfSPI4$_{1179}$, nfSPI4$_{376}$, nfSPI5$_{1492}$, nfSPI5$_{1194}$, nfSPI5$_{376}$, nfSPI6$_{1454}$, nfSPI6$_{1191}$, nfSPI6$_{376}$, nfSPI7$_{549}$, nfSPI8$_{549}$, nfSPI9$_{581}$, nfSPI10$_{654}$, nfSPI11$_{670}$, nfSPI12$_{706}$, nfSPI13$_{623}$, nfSPI14$_{731}$, nfSPI15$_{685}$, nfSPI3$_{1222}$, nfSPI6$_{1155}$, nfSPI2$_{1065}$, nfSPI4$_{1070}$, nfSPIC4:V7$_{1168}$, nfSPIC4:V8$_{1222}$, nfSPIC4:V9$_{1174}$, nfSPIC4:V10$_{1159}$, nfSPIC4:V12$_{1171}$, nfSPIC4:V13$_{1171}$, and nfSPIC4:V15$_{1179}$.

Suitable host cells to transform include any cell that can be transformed with a nucleic acid molecule of the present invention. Host cells can be either untransformed cells or cells that are already transformed with at least one nucleic acid molecule (e.g., nucleic acid molecules encoding one or more proteins of the present invention and/or other proteins useful in the production of multivalent vaccines). Host cells of the present invention either can be endogenously (i.e., naturally) capable of producing flea SPI proteins of the present invention or can be capable of producing such proteins after being transformed with at least one nucleic acid molecule of the present invention. Host cells of the present invention can be any cell capable of producing at least one protein of the present invention, and include bacterial, fungal (including yeast), other insect, other animal and plant cells. Preferred host cells include bacterial, mycobacterial, yeast, parasite, insect and mammalian cells. More preferred host cells include *Salmonella*, *Escherichia*, *Bacillus*, *Listeria*, *Saccharomyces*, *Spodoptera*, *Mycobacteria*, *Trichoplusia*, BHK (baby hamster kidney) cells, MDCK cells (normal dog kidney cell line for canine herpesvirus cultivation), CRFK cells (normal cat kidney cell line for feline herpesvirus cultivation), CV-1 cells (African monkey kidney cell line used, for example, to culture raccoon poxvirus), COS (e.g., COS-7) cells, and Vero cells. Particularly preferred host cells are *Escherichia coli*, including *E. coli* K-12 derivatives; *Salmonella typhi*; *Salmonella typhimurium*, including attenuated strains such as UK-1 $_{\chi}$3987 and SR-11 $_{\chi}$4072; *Spodoptera frugiperda*; *Trichoplusia ni*; BHK cells; MDCK cells; CRFK cells; CV-1 cells; COS cells; Vero cells; and non-tumorigenic mouse myoblast G8 cells (e.g., ATCC CRL 1246). Additional appropriate mammalian cell hosts include other kidney cell lines, other fibroblast cell lines (e.g., human, murine or chicken embryo fibroblast cell lines), myeloma cell lines, Chinese hamster ovary cells, mouse NIH/3T3 cells, LMTK^{31} cells and/or HeLa cells. In one embodiment, the proteins

may be expressed as heterologous proteins in myeloma cell lines employing immunoglobulin promoters.

A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid molecules of the present invention operatively linked to an expression vector containing one or more transcription control sequences. The phrase operatively linked refers to insertion of a nucleic acid molecule into an expression vector in a manner such that the molecule is able to be expressed when transformed into a host cell.

A recombinant molecule of the present invention is a molecule that can include at least one of any nucleic acid molecule heretofore described operatively linked to at least one of any transcription control sequence capable of effectively regulating expression of the nucleic acid molecule(s) in the cell to be transformed, examples of which are disclosed herein. Particularly preferred recombinant molecules include pλP$_R$-nfSPI2$_{1139}$, pλP$_R$-nSPI3$_{1179}$, pλP$_R$-nfSPI4$_{1140}$, pλP$_R$-nfSPI5$_{1492}$, pλP$_R$-nfSPI6$_{1136}$,pλP$_R$-nfSPIC4:V7$_{1168}$, pλP$_R$-nfSPIC4:V8$_{1222}$, pλP$_R$-nfSPIC4:V9$_{1174}$, pλP$_R$-n nfSPIC4:V10$_{1159}$, pλP$_R$-nfSPIC4:V12$_{1171}$, pλP$_R$-nfSPIC4:V13$_{1171}$, pλP$_R$-nfSPIC4:V15$_{1179}$, pVL-nfSPI3$_{1222}$, pVL-nfSPI6$_{1155}$, pAcG-nfSPI2$_{1065}$ and pAcG-nfSPI4$_{1070}$.

A recombinant cell of the present invention includes any cell transformed with at least one of any nucleic acid molecule of the present invention. Suitable and preferred nucleic acid molecules as well as suitable and preferred recombinant molecules with which to transform cells are disclosed herein. Particularly preferred recombinant cells include *E.coli*HB:pλP$_R$-nfSPI2$_{1139}$, *E.coli*HB:pλP$_R$-nfSPI3$_{1179}$, *E.coli*HB:pλP$_R$-nfSPI4$_{1140}$, *E.coli*HB:pλP$_R$-nfSPI5$_{1492}$, *E.coli*HB:pλP$_R$-nfSPI6$_{1136}$,*E.coli*:pλP$_R$-nfSPIC4:V7$_{1168}$, *E.coli*:pλP$_R$-nfSPIC4:V8$_{1222}$, *E.coli*:pλP$_R$-nfSPIC4:V9$_{1174}$, *E.coli*:pλP$_R$-nfSPIC4:V10$_{1159}$, *E.coli*:pλP$_R$-nfSPIC4:V12$_{1171}$, *E.coli*:pλP$_R$-nfSPIC4:V13$_{1171}$, *E.coli*:pλP$_R$-nfSPIC4:V15$_{1179}$, *S. frugiperda*:pVL-nfSPI3$_{1222}$, *S. frugiperda*:pVL-nfSPI6$_{1155}$, *S. frugiperda*:pAcG-nfSPI2$_{1065}$ and *S. frugiperda*:pAcG-nfSPI4$_{1070}$. Details regarding the production of these recombinant cells are disclosed herein.

Recombinant cells of the present invention can also be co-transformed with one or more recombinant molecules including flea SPI nucleic acid molecules encoding one or more proteins of the present invention and one or more other nucleic acid molecules

encoding other protective compounds, as disclosed herein (e.g., to produce multivalent vaccines).

Recombinant DNA technologies can be used to improve expression of transformed nucleic acid molecules by manipulating, for example, the number of copies of the nucleic acid molecules within a host cell, the efficiency with which those nucleic acid molecules are transcribed, the efficiency with which the resultant transcripts are translated, and the efficiency of post-translational modifications. Recombinant techniques useful for increasing the expression of nucleic acid molecules of the present invention include, but are not limited to, operatively linking nucleic acid molecules to high-copy number plasmids, integration of the nucleic acid molecules into one or more host cell chromosomes, addition of vector stability sequences to plasmids, substitutions or modifications of transcription control signals (e.g., promoters, operators, enhancers), substitutions or modifications of translational control signals (e.g., ribosome binding sites, Shine-Dalgarno sequences), modification of nucleic acid molecules of the present invention to correspond to the codon usage of the host cell, deletion of sequences that destabilize transcripts, and use of control signals that temporally separate recombinant cell growth from recombinant enzyme production during fermentation. The activity of an expressed recombinant protein of the present invention may be improved by fragmenting, modifying, or derivatizing nucleic acid molecules encoding such a protein.

Isolated SPI proteins of the present invention can be produced in a variety of ways, including production and recovery of natural proteins, production and recovery of recombinant proteins, and chemical synthesis of the proteins. In one embodiment, an isolated protein of the present invention is produced by culturing a cell capable of expressing the protein under conditions effective to produce the protein, and recovering the protein. A preferred cell to culture is a recombinant cell of the present invention. Effective culture conditions include, but are not limited to, effective media, bioreactor, temperature, pH and oxygen conditions that permit protein production. An effective medium refers to any medium in which a cell is cultured to produce a flea SPI protein of the present invention. Such medium typically comprises an aqueous medium having assimilable carbon, nitrogen and phosphate sources, and appropriate salts, minerals, metals and other nutrients, such as vitamins. Cells of the present invention can be

cultured in conventional fermentation bioreactors, shake flasks, test tubes, microtiter dishes, and petri plates. Culturing can be carried out at a temperature, pH and oxygen content appropriate for a recombinant cell. Such culturing conditions are within the expertise of one of ordinary skill in the art. Examples of suitable conditions are included in the Examples section.

Depending on the vector and host system used for production, resultant proteins of the present invention may either remain within the recombinant cell; be secreted into the fermentation medium; be secreted into a space between two cellular membranes, such as the periplasmic space in *E. coli*; or be retained on the outer surface of a cell or viral membrane. The phrase "recovering the protein", as well as similar phrases, refers to collecting the whole fermentation medium containing the protein and need not imply additional steps of separation or purification. Proteins of the present invention can be purified using a variety of standard protein purification techniques, such as, but not limited to, affinity chromatography, ion exchange chromatography, filtration, electrophoresis, hydrophobic interaction chromatography, gel filtration chromatography, reverse phase chromatography, concanavalin A chromatography, chromatofocusing and differential solubilization. Proteins of the present invention are preferably retrieved in "substantially pure" form. As used herein, "substantially pure" refers to a purity that allows for the effective use of the protein as a therapeutic composition or diagnostic. A therapeutic composition for animals, for example, should exhibit no substantial toxicity and preferably should be capable of stimulating the production of antibodies in a treated animal.

The present invention also includes isolated (i.e., removed from their natural milieu) antibodies that selectively bind to a flea SPI protein of the present invention or a mimetope thereof (i.e., anti-flea SPI antibodies). As used herein, the term "selectively binds to" a SPI protein refers to the ability of antibodies of the present invention to preferentially bind to specified proteins and mimetopes thereof of the present invention. Binding can be measured using a variety of methods standard in the art including enzyme immunoassays (e.g., ELISA), immunoblot assays, etc.; see, for example, Sambrook et al., *ibid*. An anti-flea SPI antibody preferably selectively binds to a flea SPI protein in such a way as to reduce the activity of that protein.

Isolated antibodies of the present invention can include antibodies in a bodily fluid (such as, but not limited to, serum), or antibodies that have been purified to varying degrees. Antibodies of the present invention can be polyclonal or monoclonal. Functional equivalents of such antibodies, such as antibody fragments and genetically-engineered antibodies (including single chain antibodies or chimeric antibodies that can bind to more than one epitope) are also included in the present invention.

A preferred method to produce antibodies of the present invention includes (a) administering to an animal an effective amount of a protein, peptide or mimetope thereof of the present invention to produce the antibodies and (b) recovering the antibodies. In another method, antibodies of the present invention are produced recombinantly using techniques as heretofore disclosed to produce flea SPI proteins of the present invention. Antibodies raised against defined proteins or mimetopes can be advantageous because such antibodies are not substantially contaminated with antibodies against other substances that might otherwise cause interference in a diagnostic assay or side effects if used in a therapeutic composition.

Antibodies of the present invention have a variety of potential uses that are within the scope of the present invention. For example, such antibodies can be used (a) as therapeutic compounds to passively immunize an animal in order to protect the animal from hematophagous ectoparasites susceptible to treatment by such antibodies and/or (b) as tools to screen expression libraries and/or to recover desired proteins of the present invention from a mixture of proteins and other contaminants. Furthermore, antibodies of the present invention can be used to target cytotoxic agents to hematophagous ectoparasite such as those disclosed herein in order to directly kill such hematophagous ectoparasites. Targeting can be accomplished by conjugating (i.e., stably joining) such antibodies to the cytotoxic agents using techniques known to those skilled in the art. Suitable cytotoxic agents are known to those skilled in the art.

One embodiment of the present invention is a therapeutic composition that, when administered to an animal in an effective manner, is capable of protecting that animal from infestation by hematophagous ectoparasites. Therapeutic compositions of the present invention include at least one of the following protective compounds: an isolated flea SPI protein (including a peptide of a flea SPI protein capable of inhibiting serine

protease activity), a mimetope of a flea SPI protein, an isolated SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* SPI gene, an isolated antibody that selectively binds to a flea SPI protein, and inhibitors of flea SPI activity (including flea SPI protein substrate analogs, such as serine proteases or serine protease analogs). Preferred hematophagous ectoparasites to target are heretofore disclosed. Examples of protective compounds (e.g., proteins, mimetopes, nucleic acid molecules, antibodies, and inhibitors) are disclosed herein.

Suitable inhibitors of SPI activity are compounds that interact directly with a SPI protein active site, thereby inhibiting that SPI's activity, usually by binding to or otherwise interacting with or otherwise modifying the SPI's active site. SPI inhibitors can also interact with other regions of the SPI protein to inhibit SPI activity, for example, by allosteric interaction. Inhibitors of SPIs are usually relatively small compounds and as such differ from anti-SPI antibodies. Preferably, a SPI inhibitor of the present invention is identified by its ability to bind to, or otherwise interact with, a flea SPI protein, thereby inhibiting the activity of the flea SPI.

Inhibitors of a SPI can be used directly as compounds in compositions of the present invention to treat animals as long as such compounds are not harmful to host animals being treated. Inhibitors of a SPI protein can also be used to identify preferred types of flea SPI proteins to target using compositions of the present invention, for example by affinity chromatography. Preferred inhibitors of a SPI of the present invention include, but are not limited to, flea SPI substrate analogs, and other molecules that bind to a flea SPI (e.g., to an allosteric site) in such a manner that SPI activity of the flea SPI is inhibited. A SPI substrate analog refers to a compound that interacts with (e.g., binds to, associates with, modifies) the active site of a SPI protein. A preferred SPI substrate analog inhibits SPI activity. SPI substrate analogs can be of any inorganic or organic composition, and, as such, can be, but are not limited to, peptides, nucleic acids, and peptidomimetic compounds. SPI substrate analogs can be, but need not be, structurally similar to a SPI protein's natural substrate as long as they can interact with the active site of that SPI protein. SPI substrate analogs can be designed using computer-generated structures of SPI proteins of the present invention or computer

structures of SPI proteins' natural substrates. Substrate analogs can also be obtained by generating random samples of molecules, such as oligonucleotides, peptides, peptidomimetic compounds, or other inorganic or organic molecules, and screening such samples by affinity chromatography techniques using the corresponding binding partner, (e.g., a flea SPI or anti-flea serine protease antibody). A preferred SPI substrate analog is a peptidomimetic compound (i.e., a compound that is structurally and/or functionally similar to a natural substrate of a SPI of the present invention, particularly to the region of the substrate that interacts with the SPI active site, but that inhibits SPI activity upon interacting with the SPI active site).

SPI peptides, mimetopes and substrate analogs, as well as other protective compounds, can be used directly as compounds in compositions of the present invention to treat animals as long as such compounds are not harmful to the animals being treated.

The present invention also includes a therapeutic composition comprising at least one flea SPI-based compound of the present invention in combination with at least one additional compound protective against hematophagous ectoparasite infestation. Examples of such compounds are disclosed herein.

In one embodiment, a therapeutic composition of the present invention can be used to protect an animal from hematophagous ectoparasite infestation by administering such composition to a hematophagous ectoparasite, such as to a flea, in order to prevent infestation. Such administration could be orally or by developing transgenic vectors capable of producing at least one therapeutic composition of the present invention. In another embodiment, a hematophagous ectoparasite, such as a flea, can ingest therapeutic compositions, or products thereof, present in the blood of a host animal that has been administered a therapeutic composition of the present invention.

Compositions of the present invention can be administered to any animal susceptible to hematophagous ectoparasite infestation (i.e., a host animal), including warm-blooded animals. Preferred animals to treat include mammals and birds, with cats, dogs, humans, cattle, chinchillas, ferrets, goats, mice, minks, rabbits, raccoons, rats, sheep, squirrels, swine, chickens, ostriches, quail and turkeys as well as other furry animals, pets and/or economic food animals, being more preferred. Particularly preferred animals to protect are cats and dogs.

In accordance with the present invention, a host animal (i.e., an animal that is or is capable of being infested with a hematophagous ectoparasite) is treated by administering to the animal a therapeutic composition of the present invention in such a manner that the composition itself (e.g., an inhibitor of a SPI protein, a SPI synthesis suppressor (i.e., a compound that decreases the production of SPI in the hematophagous ectoparasite), an SPI mimetope, or an anti-hematophagous ectoparasite SPI antibody) or a product generated by the animal in response to administration of the composition (e.g., antibodies produced in response to a flea SPI protein or nucleic acid molecule vaccine, or conversion of an inactive inhibitor "prodrug" to an active inhibitor of a SPI protein) ultimately enters the hematophagous ectoparasite. A host animal is preferably treated in such a way that the compound or product thereof enters the blood stream of the animal. Hematophagous ectoparasites are then exposed to the composition or product when they feed from the animal. For example, flea SPI protein inhibitors administered to an animal are administered in such a way that the inhibitors enter the blood stream of the animal, where they can be taken up by feeding fleas. In another embodiment, when a host animal is administered a flea SPI protein or nucleic acid molecule vaccine, the treated animal mounts an immune response resulting in the production of antibodies against the SPI protein (i.e., anti-flea SPI antibodies) which circulate in the animal's blood stream and are taken up by hematophagous ectoparasites upon feeding. Blood taken up by hematophagous ectoparasites enters the hematophagous ectoparasites where compounds of the present invention, or products thereof, such as anti-flea SPI antibodies, flea SPI protein inhibitors, flea mimetopes and/or SPI synthesis suppressors, interact with, and reduce SPI protein activity in the hematophagous ectoparasite.

The present invention also includes the ability to reduce larval hematophagous ectoparasite infestation in that when hematophagous ectoparasites feed from a host animal that has been administered a therapeutic composition of the present invention, at least a portion of compounds of the present invention, or products thereof, in the blood taken up by the hematophagous ectoparasite are excreted by the hematophagous ectoparasite in feces, which is subsequently ingested by hematophagous ectoparasite larvae. In particular, it is of note that flea larvae obtain most, if not all, of their nutrition from flea feces.

In accordance with the present invention, reducing SPI protein activity in a hematophagous ectoparasite can lead to a number of outcomes that reduce hematophagous ectoparasite burden on treated animals and their surrounding environments. Such outcomes include, but are not limited to, (a) reducing the viability of hematophagous ectoparasites that feed from the treated animal, (b) reducing the fecundity of female hematophagous ectoparasites that feed from the treated animal, (c) reducing the reproductive capacity of male hematophagous ectoparasites that feed from the treated animal, (d) reducing the viability of eggs laid by female hematophagous ectoparasites that feed from the treated animal, (e) altering the blood feeding behavior of hematophagous ectoparasites that feed from the treated animal (e.g., hematophagous ectoparasites take up less volume per feeding or feed less frequently), (f) reducing the viability of hematophagous ectoparasite larvae (e.g., by decreasing feeding behavior, inhibiting growth, inhibiting (e.g., slowing or blocking) molting, and/or otherwise inhibiting maturation to adults).

Therapeutic compositions of the present invention can be formulated in an excipient that the animal to be treated can tolerate. Examples of such excipients include water, saline, Ringer's solution, dextrose solution, Hank's solution, and other aqueous physiologically balanced salt solutions. Nonaqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or triglycerides may also be used. Other useful formulations include suspensions containing viscosity enhancing agents, such as sodium carboxymethylcellulose, sorbitol, or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability. Examples of buffers include phosphate buffer, bicarbonate buffer and Tris buffer, while examples of preservatives include thimerosal, — or o-cresol, formalin and benzyl alcohol. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

In one embodiment of the present invention, a therapeutic composition can include an adjuvant. Adjuvants are agents that are capable of enhancing the immune response of an animal to a specific antigen. Suitable adjuvants include, but are not

limited to, cytokines, chemokines, and compounds that induce the production of cytokines and chemokines (e.g., granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin 2 (IL-2), interleukin-3 (IL-3), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 8 (IL-8), interleukin 10 (IL-10), interleukin 12 (IL-12), interferon gamma, interferon gamma inducing factor I (IGIF), transforming growth factor beta, RANTES (regulated upon activation, normal T cell expressed and presumably secreted), macrophage inflammatory proteins (e.g., MIP-1 alpha and MIP-1 beta), and Leishmania elongation initiating factor (LEIF); bacterial components (e.g., endotoxins, in particular superantigens, exotoxins and cell wall components); aluminum-based salts; calcium-based salts; silica; polynucleotides; toxoids; serum proteins, viral coat proteins; block copolymer adjuvants (e.g., Hunter's Titermax™ adjuvant (Vaxcel™, Inc. Norcross, GA), Ribi adjuvants (Ribi ImmunoChem Research, Inc., Hamilton, MT); and saponins and their derivatives (e.g., Quil A (Superfos Biosector A/S, Denmark). Protein adjuvants of the present invention can be delivered in the form of the protein themselves or of nucleic acid molecules encoding such proteins using the methods described herein.

In one embodiment of the present invention, a therapeutic composition can include a carrier. Carriers include compounds that increase the half-life of a therapeutic composition in the treated animal. Suitable carriers include, but are not limited to, polymeric controlled release vehicles, biodegradable implants, liposomes, bacteria, viruses, other cells, oils, esters, and glycols.

One embodiment of the present invention is a controlled release formulation that is capable of slowly releasing a composition of the present invention into an animal. As used herein, a controlled release formulation comprises a composition of the present invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the present invention include liquids that, upon administration to an

animal, form a solid or a gel *in situ*. Preferred controlled release formulations are biodegradable (i.e., bioerodible).

A preferred controlled release formulation of the present invention is capable of releasing a composition of the present invention into the blood of an animal at a constant rate sufficient to attain therapeutic dose levels of the composition to protect an animal from hematophagous ectoparasite infestation. The therapeutic composition is preferably released over a period of time ranging from about 1 to about 12 months. A preferred controlled release formulation of the present invention is capable of effecting a treatment preferably for at least about 1 month, more preferably for at least about 3 months, even more preferably for at least about 6 months, even more preferably for at least about 9 months, and even more preferably for at least about 12 months.

Acceptable protocols to administer therapeutic compositions of the present invention in an effective manner include individual dose size, number of doses, frequency of dose administration, and mode of administration. Determination of such protocols can be accomplished by those skilled in the art. A suitable single dose is a dose that is capable of protecting an animal from disease when administered one or more times over a suitable time period. For example, a preferred single dose of a protein, mimetope or antibody therapeutic composition is from about 1 microgram (μg) to about 10 milligrams (mg) of the therapeutic composition per kilogram body weight of the animal. Booster vaccinations can be administered from about 2 weeks to several years after the original administration. Booster administrations preferably are administered when the immune response of the animal becomes insufficient to protect the animal from disease. A preferred administration schedule is one in which from about 10 μg to about 1 mg of the therapeutic composition per kg body weight of the animal is administered from about one to about two times over a time period of from about 2 weeks to about 12 months. Modes of administration can include, but are not limited to, subcutaneous, intradermal, intravenous, intranasal, oral, transdermal, intraocular and intramuscular routes.

According to one embodiment, a nucleic acid molecule of the present invention can be administered to an animal in a fashion to enable expression of that nucleic acid molecule into a protective protein or protective RNA (e.g., antisense RNA, ribozyme,

triple helix forms or RNA drug) in the animal. Nucleic acid molecules can be delivered to an animal in a variety of methods including, but not limited to, (a) administering a naked (i.e., not packaged in a viral coat or cellular membrane) nucleic acid vaccine (e.g., as naked DNA or RNA molecules, such as is taught, for example in Wolff et al., 1990, *Science 247*, 1465-1468) or (b) administering a nucleic acid molecule packaged as a recombinant virus vaccine or as a recombinant cell vaccine (i.e., the nucleic acid molecule is delivered by a viral or cellular vehicle).

A naked nucleic acid vaccine of the present invention includes a nucleic acid molecule of the present invention and preferably includes a recombinant molecule of the present invention that preferably is replication, or otherwise amplification, competent. A naked nucleic acid vaccine of the present invention can comprise one or more nucleic acid molecules of the present invention in the form of, for example, a bicistronic recombinant molecule having, for example one or more internal ribosome entry sites. Preferred naked nucleic acid vaccines include at least a portion of a viral genome (i.e., a viral vector). Preferred viral vectors include those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, and retroviruses, with those based on alphaviruses (such as Sindbis or Semliki virus), species-specific herpesviruses and species-specific poxviruses being particularly preferred. Any suitable transcription control sequence can be used, including those disclosed as suitable for protein production. Particularly preferred transcription control sequence include cytomegalovirus intermediate early (preferably in conjunction with Intron-A), Rous Sarcoma Virus long terminal repeat, and tissue-specific transcription control sequences, as well as transcription control sequences endogenous to viral vectors if viral vectors are used. The incorporation of "strong" poly(A) sequences are also preferred.

Naked nucleic acid vaccines of the present invention can be administered in a variety of ways, with intramuscular, subcutaneous, intradermal, transdermal, intranasal and oral routes of administration being preferred. A preferred single dose of a naked nucleic acid vaccines ranges from about 1 nanogram (ng) to about 100 μg, depending on the route of administration and/or method of delivery, as can be determined by those skilled in the art. Suitable delivery methods include, for example, by injection, as drops, aerosolized and/or topically. Naked DNA of the present invention can be contained in

an aqueous excipient (e.g., phosphate buffered saline) alone or a carrier (e.g., lipid-based vehicles).

A recombinant virus vaccine of the present invention includes a recombinant molecule of the present invention that is packaged in a viral coat and that can be expressed in an animal after administration. Preferably, the recombinant molecule is packaging-deficient and/or encodes an attenuated virus. A number of recombinant viruses can be used, including, but not limited to, those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, and retroviruses. Preferred recombinant virus vaccines are those based on alphaviruses (such as Sindbis virus), raccoon poxviruses, species-specific herpesviruses and species-specific poxviruses. An example of methods to produce and use alphavirus recombinant virus vaccines is disclosed in PCT Publication No. WO 94/17813, by Xiong et al., published August 18, 1994, which is incorporated by reference herein in its entirety.

When administered to an animal, a recombinant virus vaccine of the present invention infects cells within the immunized animal and directs the production of a protective protein or RNA nucleic acid molecule that is capable of protecting the animal from hematophagous ectoparasite infestation. For example, a recombinant virus vaccine comprising a flea SPI nucleic acid molecule of the present invention is administered according to a protocol that results in the animal producing a sufficient immune response to protect itself from hematophagous ectoparasite infestation. A preferred single dose of a recombinant virus vaccine of the present invention is from about 1×10^4 to about 1×10^7 virus plaque forming units (pfu) per kilogram body weight of the animal. Administration protocols are similar to those described herein for protein-based vaccines, with subcutaneous, intramuscular, intranasal and oral administration routes being preferred.

A recombinant cell vaccine of the present invention includes recombinant cells of the present invention that express at least one protein of the present invention. Preferred recombinant cells for this embodiment include *Salmonella*, *E. coli*, *Listeria*, *Mycobacterium*, *S. frugiperda*, yeast, (including *Saccharomyces cerevisiae*), BHK, CV-1, myoblast G8, COS (e.g., COS-7), Vero, MDCK and CRFK recombinant cells. Recombinant cell vaccines of the present invention can be administered in a variety of

ways but have the advantage that they can be administered orally, preferably at doses ranging from about 10^8 to about 10^{12} cells per kilogram body weight. Administration protocols are similar to those described herein for protein-based vaccines. Recombinant cell vaccines can comprise whole cells, cells stripped of cell walls or cell lysates.

The efficacy of a therapeutic composition of the present invention to protect an animal from hematophagous ectoparasite infestation can be tested in a variety of ways including, but not limited to, detection of anti-flea SPI antibodies (using, for example, proteins or mimetopes of the present invention), detection of cellular immunity within the treated animal, or challenge of the treated animal with hematophagous ectoparasites to determine whether, for example, the feeding, fecundity or viability of the hematophagous ectoparasites feeding from the treated animal is disrupted. Challenge studies can include attachment of chambers containing fleas onto the skin of the treated animal. In one embodiment, therapeutic compositions can be tested in animal models such as mice. Such techniques are known to those skilled in the art.

One preferred embodiment of the present invention is the use of flea SPI proteins, mimetopes, nucleic acid molecules, antibodies and inhibitory compounds of the present invention, to protect an animal from hematophagous ectoparasite infestation. Preferred protective compounds of the present invention include, but are not limited to, an isolated flea SPI protein or a mimetope thereof, an isolated SPI nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* SPI gene, an isolated antibody that selectively binds to a flea SPI and/or an inhibitor of flea SPI activity (such as, but not limited to, an SPI substrate analog). Additional protection may be obtained by administering additional protective compounds, including other proteins, nucleic acid molecules, antibodies and inhibitory compounds, as disclosed herein.

An inhibitor of SPI activity can be identified using flea SPI proteins of the present invention. One embodiment of the present invention is a method to identify a compound capable of inhibiting SPI activity of a flea. Such a method includes the steps of (a) contacting (e.g., combining, mixing) an isolated flea SPI protein, preferably a *C. felis* SPI protein, with a putative inhibitory compound under conditions in which, in the absence of the compound, the protein has SPI activity, and (b) determining if the

putative inhibitory compound inhibits the SPI activity. Putative inhibitory compounds to screen include small organic molecules, antibodies (including mimetopes thereof) and substrate analogs. Methods to determine SPI activity are known to those skilled in the art.

The present invention also includes a test kit to identify a compound capable of inhibiting SPI activity of a flea. Such a test kit includes an isolated flea SPI protein, preferably a *C. felis* SPI protein, having SPI activity and a means for determining the extent of inhibition of SPI activity in the presence of (i.e., effected by) a putative inhibitory compound. Such compounds are also screened to identify those that are substantially not toxic in host animals.

SPI inhibitors isolated by such a method, and/or test kit, can be used to inhibit any SPI protein that is susceptible to such an inhibitor. Preferred SPI enzymes proteins to inhibit are those produced by fleas. A particularly preferred inhibitor of a SPI protein of the present invention is capable of protecting an animal from flea infestation. Effective amounts and dosing regimens can be determined using techniques known to those skilled in the art.

The following examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention.

EXAMPLES

It is to be noted that the Examples include a number of molecular biology, microbiology, immunology and biochemistry techniques considered to be known to those skilled in the art. Disclosure of such techniques can be found, for example, in Sambrook et al., *ibid.*, and related references.

Example 1

This example describes the isolation of a protein fraction from flea prepupal larvae that was obtained by monitoring for carboxylesterase activity, which surprisingly, also contained flea serine protease inhibitor molecule epitopes of the present invention, discovered as described in Examples 2, 3 and 4 below.

A prepupal larval protein pool enriched for carboxylesterase activity was isolated as follows. About 17,000 bovine blood-fed prepupal larvae were collected and the larvae were homogenized in gut dissection buffer (50 mM Tris pH 8.0, 100 mM $CaCl_2$)

by sonication in a disposable 50 ml conical centrifuge tube. Sonication entailed 4 bursts of 20 seconds each at a setting of 4 with a probe sonicator using, for example, a model W-380 Sonicator (available from Heat Systems-Ultrasonics, Inc., Farmingdale, NY). The sonicate was clarified by centrifugation at 4000 rpm for 30 min. in a swinging bucket centrifuge; the supernatant was collected and centrifuged at 18,000 rpm for 30 min in a Sorvall SS-34 rotor (available from DuPont, Wilmington, DE). The supernatant was recovered, and NaCl was added to a final concentration of 400 mM.

Serine proteases were removed from the supernatant using the following method. The supernatant was loaded onto a 5-ml column comprising p-aminobenzamidine cross-linked to Sepharose beads (available from Sigma Chemical Company, St. Louis, MO), previously equilibrated in benzamidine column buffer (50 mM Tris 8.0, 100 mM $CaCl_2$, 400 mM NaCl) and incubated overnight at 4°C. Unbound protein was slowly washed off and collected from the column with benzamidine column buffer until no protein was detectable by a Bradford Assay (available from Bio-Rad Laboratories, Hercules, CA). A total of about 43 ml was collected. The proteins in this pool were fractionated by precipitation in increasing percent saturation levels of ammonium sulfate.

The ammonium sulfate-precipitated protein fractions, as well as all subsequent protein fractions described in this example, were assayed for carboxylesterase activity by the following method. Samples of about 5 μl of each fraction were added to separate wells of a flat-bottomed microtiter plate (available from Becton Dickinson, Lincoln Park, NJ). A control well was prepared by adding about 5 μl of Tris buffer to an empty well of the plate. About 95 μl of 25 mM Tris-HCl (pH 8.0) was then added to each sample to increase the volume in each well to about 100 μl. About 100 μl of 0.25 mM α-napthyl acetate (available from Sigma) dissolved in 25 mM Tris-HCl (pH 8.0) was then added to each well. The plate was then incubated for about 15 min. at 37°C. Following the incubation, about 40 μl of 0.3% Fast Blue salt BN (tetrazotized o-dianisidine; available from Sigma), dissolved in 3.3% SDS in water was added to each well, giving a colorimetric reaction. Absorbance levels were measured using a model 7500 Microplate Reader (available from Cambridge Technology, Inc., Watertown, MA) set to 590 nm. Following subtraction of background absorbance, the resulting values gave a relative measure of carboxylesterase activity. Carboxylesterase activity was found

in two of the ammonium sulfate-precipitated fractions. The first, which precipitated between about 0 and 60% ammonium sulfate saturation, was kept as a pool, and the second, which precipitated between about 60 and 80% ammonium sulfate saturation, was kept separately as a pool. Since the latter pool appeared to have higher activity at this point, the pools were treated separately until just prior to the final HPLC step described below, but at that point they were combined.

The two ammonium sulfate-precipitated protein pools were then subjected to cation exchange chromatography, performed as follows. Each protein pool was dialyzed two times against about 500 ml of 20 mM 2-(N-morpholino) ethanesulfonic acid (MES) buffer, pH 6, containing 10 mM NaCl and was then applied to a 40-ml chromatography column containing 10 ml of S-Sepharose Fast Flow cation exchange resin (available from Pharmacia Biochemicals, Piscataway, NJ), previously equilibrated with MES buffer. Each column was rocked overnight at 4°C to facilitate protein binding, and was then drained and washed with more MES buffer to remove all unbound protein in about 40 ml total volume. Following elution of the bound proteins, the bound and unbound protein fractions were tested for carboxylesterase activity as described above. Activity was found to reside in the unbound protein fractions from each column, which were then concentrated to about 5 ml using Centriprep® 30 centrifugal concentrators (available from Amicon, Beverly, MA).

The two concentrated protein pools were then subjected to anion exchange chromatography, performed as follows. Each pool was adjusted to about pH 7 by the addition of a small amount of 500 mM Tris buffer, pH 8, and was then applied, in about 1 to 1.5 ml aliquots, to a 4.5 mm x 50 mm Poros 10 HQ anion exchange chromatography column (available from PerSeptive Biosystems, Cambridge, MA) equilibrated in 25 mM Tris, pH 6.8 (loading buffer). For each aliquot, the column was washed with the loading buffer, and bound proteins were eluted with a linear gradient of 0 to 1 M NaCl in 25 mM Tris buffer, pH 6.8. All column fractions were tested for carboxylesterase activity as described above. For each aliquot run on the column, the activity peak eluted in fractions 31-34, and at this point in the isolation, the activity levels appeared to be equivalent in both of the original ammonium sulfate-fractionated pools. Therefore, all

column fractions containing carboxylesterase activity were combined into one pool. This pool was concentrated and diafiltered into about 1 ml of Tris-buffered saline (TBS).

The pooled protein preparation was then loaded onto a C1 reverse phase HPLC column (available from TosoHaas, Montgomeryville, PA), previously equilibrated with 19% acetonitrile containing 0.05% trifluoroacetic acid (TFA). The column was washed with the equilibration buffer to remove unbound proteins, and bound proteins were eluted from the column by a linear gradient from 19% acetonitrile containing 0.05% TFA to 95% acetonitrile containing 0.05% TFA. The column fractions were tested for carboxylesterase activity as described above, and the activity peak eluted in fractions 27-32. These fractions were combined, concentrated to near dryness using a Speed-Vac™ concentrator (available from Savant Instruments, Molbrook, NY), and resuspended in phosphate-buffered saline (PBS) to a concentration of about 0.2mg/ml. This isolated protein fraction is referred to herein as flea prepupal carboxylesterase fraction-1. Upon analysis by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and silver staining, flea prepupal carboxylesterase fraction-1 appeared to contain, in addition to the recognized carboxylesterase bands migrating at about 60 kD, a strong protein band migrating at about 40 kD.

Example 2

This example describes the generation of polyclonal rabbit antiserum to flea prepupal carboxylesterase fraction-1.

Antibodies against flea prepupal carboxylesterase fraction-1 (the preparation of which is described in Example 1) were generated as follows. A rabbit was initially immunized subcutaneously and intradermally at multiple sites with a total of approximately 50 μg of flea prepupal carboxylesterase fraction-1 emulsified in Complete Freund's Adjuvant. On days 16 and 37 after the initial immunization, the rabbit was boosted intramuscularly with a total of approximately 50 μg of flea prepupal carboxylesterase fraction-1emulsified in Incomplete Freund's Adjuvant. The rabbit was bled on days 9, 29 and 50 after the initial immunization. Sera from the latter two bleeds, putatively containing antibodies to flea prepupal carboxylesterases, were used separately for immunoscreening experiments, as described in Example 3 below.

Example 3

This example describes the isolation, by immunoscreening, of nucleic acid molecules encoding flea serine protease inhibitor proteins of the present invention.

Surprisingly, six flea serine protease inhibitor nucleic acid molecules were isolated by their ability to encode proteins that selectively bound to at least one component of the immune serum collected from a rabbit immunized with flea prepupal carboxylesterase fraction-1, using the following method. A flea prepupal cDNA library was produced as follows. Total RNA was extracted from approximately 3,653 prepupal larvae using an acid-guanidinium-phenol-chloroform method similar to that described by Chomczynski et al., 1987, *Anal. Biochem. 162*, 156-159. Poly A+ selected RNA was separated from the total RNA preparation by oligo-dT cellulose chromatography using Poly(A)Quick® mRNA isolation kits (available from Stratagene Cloning Systems, La Jolla, CA), according to the method recommended by the manufacturer. A prepupal cDNA expression library was constructed in lambda Uni-ZAP™XR vector (available from Stratagene), using Stratagene's ZAP-cDNA Synthesis Kit® protocol. About 6.72 μg of prepupal poly A+ RNA was used to produce the prepupal library. The resultant prepupal library was amplified to a titer of about 3.5 x 10^{10} pfu/ml with about 97% recombinants.

Using a modification of the protocol described in the picoBlue immunoscreening kit (available from Stratagene), the pre-pupal cDNA expression library was screened with the flea prepupal carboxylesterase fraction-1 immune rabbit serum, generated as described in Example 2. The protocol was modified in that the secondary peroxidase-conjugated antibody was detected with a chromogen substrate consisting of DAB (3,3' diaminobenzidine) plus cobalt (Sigma Fast, available from Sigma) following the manufacturer's instructions, except that tablets were dissolved in water at one half the recommended final concentration. Plaque lift membranes were placed in the substrate solution for about 2 minutes, rinsed in water, and then dried at room temperature. Immunoscreening of duplicate plaque lifts of the cDNA library with the same immune rabbit serum identified six clones containing flea nucleic acid molecules $nfSPI1_{1584}$, $nfSPI2_{1358}$, $nfSPI3_{1838}$, $nfSPI4_{1414}$, $nfSPI5_{1492}$, and $nfSPI6_{1454}$, respectively. Plaque purified clones including the flea nucleic acid molecules were converted into double

stranded recombinant molecules, herein denoted as pβgal-nfSPI1$_{1584}$, pβgal-nfSPI2$_{1358}$, pβgal-nfSPI3$_{1838}$, pβgal-nfSPI4$_{1414}$, pβgal-nfSPI5$_{1492}$, and pβgal-nfSPI6$_{1454}$, using ExAssist^{tm} helper phage and SOLR^{tm} *E. coli* according to the *in vivo* excision protocol described in the Zap-cDNA Synthesis Kit (available from Stratagene). Double-stranded plasmid DNA was prepared using an alkaline lysis protocol, such as that described in Sambrook et al., *ibid.*

Example 4

This example describes the sequencing of several flea serine protease inhibitor nucleic acid molecules of the present invention.

The plasmids containing flea nfSPI1$_{1584}$, nfSPI2$_{1358}$, nfSPI3$_{1838}$, nfSPI4$_{1414}$, nfSPI5$_{1492}$, and nfSPI6$_{1454}$ were sequenced by the Sanger dideoxy chain termination method, using the PRISM™ Ready Dye Terminator Cycle Sequencing Kit with AmpliTaq® DNA Polymerase, FS (available from the Perkin-Elmer Corporation, Norwalk, CT). PCR extensions were done in the GeneAmp™ PCR System 9600 (available from Perkin-Elmer). Excess dye terminators were removed from extension products using the Centriflex™ Gel Filtration Cartridge (available from Advanced Genetics Technologies Corporation, Gaithersburg, MD) following their standard protocol. Samples were resuspended according to ABI protocols and were and run on a Perkin-Elmer ABI PRISM™ 377 Automated DNA Sequencer. DNA sequence analyses, including the compilation of sequences and the determination of open reading frames, were performed using either the DNAsis™ program (available from Hitachi Software, San Bruno, CA) or the MacVector™ program (available from the Eastman Kodak Company, New Haven, CT). Protein sequence analyses, including the determination of molecular weights and isoelectric points (pI) were performed using the MacVector™ program.

A. An about 1584-nucleotide consensus sequence of the entire flea nfSPI1$_{1584}$ DNA fragment was determined; the sequences of the two complementary strands are presented as SEQ ID NO:1 (the coding strand) and SEQ ID NO:3 (the complementary strand). The flea nfSPI1$_{1584}$ sequence contains a full length coding region. The apparent start and stop codons span nucleotides from about 136 through about 138 and from about 1327 through about 1329, respectively, of SEQ ID NO:1. A putative

polyadenylation signal (5' AATAAA 3') is located in a region spanning from about nucleotide 1533 through about 1538 of SEQ ID NO:1.

Translation of SEQ ID NO:1 yields a protein of about 397 amino acids, denoted $PfSPI1_{397}$, the amino acid sequence of which is presented in SEQ ID NO:2. The nucleic acid molecule consisting of the coding region encoding $PfSPI1_{397}$ is referred to herein as $nfSPI1_{1191}$, the nucleic acid sequence of which is represented in SEQ ID NO:4 (the coding strand) and SEQ ID NO:5 (the complementary strand). The amino acid sequence of flea $PfSPI1_{397}$ (i.e., SEQ ID NO:2) predicts that $PfSPI1_{397}$ has an estimated molecular weight of about 44.4 kD and an estimated pI of about 4.97. Analysis of SEQ ID NO:2 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 21. The proposed mature protein, denoted herein as $PfSPI1_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:6. The amino acid sequence of flea $PfSPI1_{376}$ (i.e. SEQ ID NO:6) predicts that $PfSPI1_{376}$ has an estimated molecular weight of about 42.1 kD, an estimated pI of about 4.90, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

Homology searches of the non-redundant protein and nucleotide sequence databases were performed through the National Center for Biotechnology Information using the BLAST network. The protein database includes SwissProt +PIR + SPUpdate + Genpept + GPUpdate. The nucleotide database includes GenBank + EMBL + DDBJ + PDB. The protein search was performed using SEQ ID NO:2, which showed significant homology to certain serine protease inhibitor proteins. The highest scoring match of the homology search at the amino acid level was GenBank accession number 1378131: *Manduca sexta*, which was about 36% identical with SEQ ID NO:2. At the nucleotide level, the search was performed using SEQ ID NO:4, which was most similar to accession number L20792, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 2) of *Manduca sexta*, being about 55% identical.

B. An about 1358-nucleotide consensus sequence of the entire flea $nfSPI2_{1358}$ DNA fragment was determined; the sequences of the two complementary strands are presented as SEQ ID NO:7 (the coding strand) and SEQ ID NO:9 (the complementary strand). The flea $nfSPI2_{1358}$ sequence contains a partial coding region, which is truncated

at the 5' end. The first in-frame codon spans nucleotides from 2 through 4 and the stop codon spans nucleotides from 1199 through 1201 of SEQ ID NO:7.

Translation of SEQ ID NO:7 yields a protein of about 399 amino acids, denoted $PfSPI2_{399}$, the amino acid sequence of which is presented in SEQ ID NO:8. The nucleic acid molecule consisting of the coding region encoding $PfSPI2_{399}$ is referred to herein as $nfSPI2_{1197}$, the nucleic acid sequence of which is represented in SEQ ID NO:10 (the coding strand) and SEQ ID NO:11 (the complementary strand). Analysis of SEQ ID NO:8 suggests the presence of a partial signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 23. The proposed mature protein, denoted herein as $PfSPI2_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:12. The amino acid sequence of flea $PfSPI1_{376}$ (i.e. SEQ ID NO:12) predicts that $PfSPI2_{376}$ has an estimated molecular weight of about 42.1 kD, an estimated pI of about 4.87, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

BLAST searches were performed as described in Section A. The protein search was performed using SEQ ID NO:8, which showed significant homology to certain serine protease inhibitor proteins. The highest scoring match of the homology search at the amino acid level was GenBank accession number 1345616: *Homo sapiens*, which was about 36% identical with SEQ ID NO:8. At the nucleotide level, the search was performed using SEQ ID NO:10, which was most similar to accession number L20790, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 1) of *Manduca sexta*, being about 43% identical.

C. An about 1838-nucleotide consensus sequence of the entire flea $nfSPI3_{1838}$ DNA fragment was determined; the sequences of the two complementary strands are presented as SEQ ID NO:13 (the coding strand) and SEQ ID NO:15 (the complementary strand). The flea $nfSPI3_{1838}$ sequence contains a full-length coding region. The apparent start and stop codons span nucleotides from about 306 through about 308 and from about 1566 through about 1568, respectively, of SEQ ID NO:13. A putative polyadenylation signal (5' AATAAA 3') is located in a region spanning from about nucleotide 1803 through about 1808 of SEQ ID NO:13.

Translation of SEQ ID NO:13 yields a protein of about 420 amino acids, denoted $PfSPI3_{420}$, the amino acid sequence of which is presented in SEQ ID NO:14. The nucleic acid molecule consisting of the coding region encoding $PfSPI3_{420}$ is referred to herein as $nfSPI3_{1260}$, the nucleic acid sequence of which is represented in SEQ ID NO:16 (the coding strand) and SEQ ID NO:17 (the complementary strand). The amino acid sequence of flea $PfSPI3_{420}$ (i.e., SEQ ID NO:14) predicts that $PfSPI3_{420}$ has an estimated molecular weight of about 47.1 kD and an estimated pI of about 4.72. Analysis of SEQ ID NO:14 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 30. The proposed mature protein, denoted herein as $PfSPI3_{390}$, contains about 390 amino acids which is represented herein as SEQ ID NO:18. The amino acid sequence of flea $PfSPI3_{390}$ (i.e. SEQ ID NO:18) predicts that $PfSPI3_{390}$ has an estimated molecular weight of about 43.7 kD, an estimated pI of about 4.63, and two predicted asparagine-linked glycosylation sites extending from about amino acid 252 to about amino acid 254 and from about amino acid 369 to about amino acid 371.

BLAST searches were performed as described in Section A. The protein search was performed using SEQ ID NO:14, which showed significant homology to certain serine protease inhibitor proteins. The highest scoring match of the homology search at the amino acid level was GenBank accession number 1345616: *Homo sapiens*, which was about 35% identical with SEQ ID NO:14. At the nucleotide level, the search was performed using SEQ ID NO:16, which was most similar to accession number L20792, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 2) of *Manduca sexta*, being about 52% identical.

D. An about 1414-nucleotide consensus sequence of the entire flea $nfSPI4_{1414}$ DNA fragment was determined; the sequences of the two complementary strands are presented as SEQ ID NO:19 (the coding strand) and SEQ ID NO:21(the complementary strand). The flea $nfSPI4_{1414}$ sequence contains a partial coding region, truncated at the 5' end. The first in-frame codon spans nucleotides from 2 through 4 and the stop codon spans nucleotides from 1181 through 1183 of SEQ ID NO:19. A putative polyadenylation signal (5' AATAAA 3') is located in a region spanning from nucleotide 1179 through 1184 of SEQ ID NO:19.

Translation of SEQ ID NO:19 yields a protein of about 393 amino acids, denoted $PfSPI4_{393}$, the amino acid sequence of which is presented in SEQ ID NO:20. The nucleic acid molecule consisting of the coding region encoding $PfSPI4_{393}$ is referred to herein as $nfSPI4_{1179}$, the nucleic acid sequence of which is represented in SEQ ID NO:22 (the coding strand) and SEQ ID NO:23 (the complementary strand). Analysis of SEQ ID NO:20 suggests the presence of a partial signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 17. The proposed mature protein, denoted herein as $PfSPI4_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:24. The amino acid sequence of flea $PfSPI4_{376}$ (i.e. SEQ ID NO:24) predicts that $PfSPI4_{376}$ has an estimated molecular weight of about 42.2 kD, an estimated pI of about 5.31, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

BLAST searches were performed as described in Section A. The protein search was performed using SEQ ID NO:20, which showed significant homology to certain serine protease inhibitor proteins. The highest scoring match of the homology search at the amino acid level was GenBank accession number 1345616: *Homo sapiens*, which was about 38% identical with SEQ ID NO:20. At the nucleotide level, the search was performed using SEQ ID NO:22, which was most similar to accession number L20793, a putative serine proteinase inhibitor gene (serpin 1, exon 9 unknown copy number) of *Manduca sexta*, being about 55% identical.

E. An about 1492-nucleotide consensus sequence of the entire flea $nfSPI5_{1492}$ DNA fragment was determined; the sequences of the two complementary strands are presented as SEQ ID NO:25 (the coding strand) and SEQ ID NO:27 (the complementary strand). The flea $nfSPI5_{1492}$ sequence contains a partial coding region, truncated at the 5' end. The first in-frame codon spans nucleotides from 3 through 5 and the stop codon spans nucleotides from 1197 through 1199 of SEQ ID NO:25. A putative polyadenylation signal (5' AATAAA 3') is located in a region spanning from nucleotide 1416 through 1421 of SEQ ID NO:25.

Translation of SEQ ID NO:25 yields a protein of about 398 amino acids, denoted $PfSPI5_{398}$, the amino acid sequence of which is presented in SEQ ID NO:26. The nucleic acid molecule consisting of the coding region encoding $PfSPI5_{398}$ is referred to

herein as $nfSPI5_{1194}$, the nucleic acid sequence of which is represented in SEQ ID NO:28 (the coding strand) and SEQ ID NO:29 (the complementary strand). Analysis of SEQ ID NO:26 suggests the presence of a partial signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 22. The proposed mature protein, denoted herein as $PfSPI5_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:30. The amino acid sequence of flea $PfSPI5_{376}$ (i.e. SEQ ID NO:30) predicts that $PfSPI5_{376}$ has an estimated molecular weight of about 42.3 kD, an estimated pI of about 5.31 and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

BLAST searches were performed as described in Section A. The protein search was performed using SEQ ID NO:26, which showed significant homology to certain serine protease inhibitor proteins. The highest scoring match of the homology search at the amino acid level was GenBank accession number 1345616: *Homo sapiens*, which was about 38% identical with SEQ ID NO:26. At the nucleotide level, the search was performed using SEQ ID NO:28, which was most similar to accession number L20790, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 1) of *Manduca sexta*, being about 45% identical.

F. An about 1454-nucleotide consensus sequence of the entire flea $nfSPI6_{1454}$ DNA fragment was determined; the sequences of the two complementary strands are presented as SEQ ID NO:31 (the coding strand) and SEQ ID NO:33 (the complementary strand). The flea $nfSPI6_{1454}$ sequence contains a full length coding region. The apparent start and stop codons span nucleotides from about 20 through about 22 and from about 1211 through about 1213, respectively, of SEQ ID NO:31. A putative polyadenylation signal (5' AATAAA 3') is located in a region spanning from about nucleotide 1419 through about 1424 of SEQ ID NO:31.

Translation of SEQ ID NO:31 yields a protein of about 397 amino acids, denoted $PfSPI6_{397}$, the amino acid sequence of which is presented in SEQ ID NO:32. The nucleic acid molecule consisting of the coding region encoding $PfSPI6_{397}$ is referred to herein as $nfSPI6_{1191}$, the nucleic acid sequence of which is represented in SEQ ID NO:34 (the coding strand) and SEQ ID NO:35 (the complementary strand). The amino acid sequence of flea $PfSPI6_{397}$ (i.e., SEQ ID NO:32) predicts that $PfSPI6_{397}$ has an estimated

molecular weight of about 44.4 kD and an estimated pI of about 4.90. Analysis of SEQ ID NO:32 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 21. The proposed mature protein, denoted herein as $PfSPI6_{376}$, contains about 376 amino acids which is represented herein as SEQ ID NO:36. The amino acid sequence of flea $PfSPI6_{376}$ (i.e. SEQ ID NO:36) predicts that $PfSPI6_{376}$ has an estimated molecular weight of about 42.1 kD, an estimated pI of about 4.84, and a predicted asparagine-linked glycosylation site extending from about amino acid 252 to about amino acid 254.

BLAST searches were performed as described in Section A. The protein search was performed using SEQ ID NO:32, which showed significant homology to certain serine protease inhibitor proteins. The highest scoring match of the homology search at the amino acid level was GenBank accession number 1378131: *Manduca sexta*, which was about 36% identical with SEQ ID NO:32. At the nucleotide level, the search was performed using SEQ ID NO:34, which was most similar to accession number L20792, a putative serine proteinase inhibitor gene (serpin 1, exon 9 copy 2) of *Manduca sexta*, being about 55% identical.

Example 5

This example discloses the production of a several recombinant cells of the present invention.

A. Recombinant molecule $p\lambda P_R$-$nfSPI2_{1139}$, containing a portion of a flea serine protease inhibitor molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1185-nucleotide DNA fragment containing nucleotides spanning from about 26 through about 1202 of SEQ ID NO:7, denoted herein as $nfSPI2_{1185}$, was PCR amplified from nucleic acid molecule $nfSPI2_{1358}$, produced as described in Example 3, using sense primer JPI5, having the nucleic acid sequence 5' GTG TTT CTT TTT GTA TCA GTG 3', denoted as SEQ ID NO:37, and antisense primer, JPI18, having the nucleic acid sequence 5' **CGG AAT TC**T TTA AAG GGA TTT AAC AC 3' (*Eco*RI site in bold), denoted SEQ ID NO:38. The amplified gene sequence contained a natural *Bam*HI site about 24 bp downstream of the 3' end of JPI5 that was used for subcloning into the expression vector. Recombinant

molecule pλP_R-nfSPI2$_{1139}$ was produced by digesting nfSPI2$_{1185}$-containing PCR product with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, the production of which is described in PCT Publication No. US95/02941, by Tripp et al., published 9/14/95, Example 7, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified.

Recombinant molecule pλP_R-nfSPI2$_{1139}$ was transformed into *E. coli* strain HB101 competent cells (available from Gibco/BRL, Gaithersburg, MD) to form recombinant cell *E.coli*:pλP_R-nfSPI2$_{1139}$ using standard techniques as disclosed in Sambrook, et al., *ibid.*

The recombinant cells were cultured in enriched bacterial growth medium containing 0.1 mg/ml ampicillin and 0.1% glucose at about 32°C. When the cells reached an OD_{600} of about 0.4-0.5, expression of recombinant protein was induced under heat shift conditions in which the cells were grown at 32°C for about 2 hours, and then grown at 42°C. Immunoblot analysis of recombinant cell *E.coli*:pλP_R-nfSPI2$_{1139}$ lysates using the T7 tag monoclonal antibody (available from Novagen, Inc., Madison, WI) directed against the fusion portion of the recombinant PHis-PfSPI2$_{376}$ fusion protein identified proteins of appropriate size, namely an about 41 kD protein for each fusion protein.

Expression of the recombinant PHis-PfSPI2$_{376}$ fusion protein was improved by transforming supercoiled plasmid pλP_R-nfSPI2$_{1139}$ DNA harvested from *E.coli*:pλP_R-nfSPI2$_{1139}$ cells into the BL-21 strain of *E. coli* (available from Novagen). The amount of expression of PHis-PfSPI2$_{376}$ was confirmed by immunoblot using the method described immediately above.

E. coli cells expressing recombinant protein PHis-PfSPI2$_{376}$ were harvested from about 1 liter of media and suspended in about 40 ml of 50 mM Tris, pH 8, 50 mM NaCl, and 1 mg lysozyme (Lysis Buffer). The cells incubated in an ice bath for about 30 minutes (min) and then were centrifuged at about 30,000 x g for 30 min at 4°C. The supernatant (S1) was recovered and the pellet resuspended in about 40 ml Lysis Buffer containing 0.1% Triton X-100 and centrifuged at about 30,000 x g for 30 min at 4°C. The supernatant (S2) was recovered and the pellet resuspended in about 20 ml of

phosphate buffered saline (PBS) containing 8 M urea (S3). Aliquots of each supernatant were analyzed by SDS-PAGE and immunoblot using a T7 tag monoclonal antibody (available from Novagen, Inc., Madison, WI). The results indicated that the PHis-$PfSPI2_{376}$ protein was located in the final supernatant (S3). The PHis-$PfSPI2_{376}$ was loaded onto a 5 ml, metal chelating HiTrap™ column charged with $NiCl_2$ (available from Pharmacia Biotech Inc., Piscataway, NJ), previously equilibrated with PBS containing 8 M urea. The column was washed with PBS containing 8 M urea until all unbound protein was removed. Bound PHis-$PfSPI2_{376}$ protein was eluted with linear gradient from 0 to 1 M imidazole in PBS containing 8 M urea. Column fractions were analyzed for the presence of PHis-$PfSPI2_{376}$ by SDS-PAGE and immunoblot using a T7 tag monoclonal antibody. The results indicated that PHis-$PfSPI2_{376}$ was eluted at about 300 mM imidazole. The column fractions containing PHis-$PfSPI2_{376}$ protein were combined and diluted in 20 mM Tris, pH 8 containing 8 M urea in preparation for anion exchange chromatography. The sample was then loaded onto a 4.5 mm x 50 mm Poros 10 HQ anion exchange chromatography column (available from PerSeptive Biosystems, Framingham, MA), previously equilibrated with 20 mM Tris, pH 8 containing 8 M urea. Unbound proteins were washed from the column using the same buffer. Bound proteins were eluted with a linear gradient of from 0 to 1 M NaCl in 20 mM Tris, pH 8 containing 8 M urea. Column fractions were analyzed for the presence of PHis-$PfSPI2_{376}$ by SDS-PAGE. The results indicated that PHis-$PfSPI2_{376}$ was eluted at about 500 mM NaCl.

The purified PHis-$PfSPI2_{376}$ protein was used to produce an anti-SPI2 polyclonal antiserum as follows. Fractions containing PHis-$PfSPI2_{376}$ protein were combined and diluted to a concentration of about 0.1 mg/ml in PBS. A rabbit was immunized and boosted with about 1 mL of a 1:1 mix of antigen and adjuvant. The primary immunization was performed using antigen combined with Complete Freunds Adjuvant. About 500 μl of the mixture was injected subcutaneously into 5 different sites (0.1 ml/site) and 500 μl was injected intradermally into 5 different sites (0.1 ml/site) of the rabbit. Boosts were administered using antigen combined with Incomplete Freunds Adjuvant and were given on days 14 and 36 after the primary immunization, in 250 μl/site doses, intramuscularly, in 4 different sites. Blood samples were obtained prior to

immunization (pre-bleed), and approximately every two weeks after the primary immunization. Serum samples from the pre-immunization and days 27, 41, and 55 after the primary immunization were used for subsequent immunoblot experiments.

B. Recombinant molecule pλP$_R$-nfSPI3$_{1179}$, containing a portion of a flea serine protease inhibitor molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1225-nucleotide DNA fragment containing nucleotides spanning from about 351 through about 1570 of SEQ ID NO:13, denoted herein as nfSPI3$_{1225}$, was PCR amplified from nucleic acid molecule nfSPI3$_{1838}$, produced as described in Example 3, using sense primer JPI5 (SEQ ID NO:37), and antisense primer was JPI15, having the nucleic acid sequence 5' CGG **AAT TCT** AAT TGG TAA ATC TC 3' (*Eco*RI site in bold), denoted SEQ ID NO:39. The amplified gene sequence contained a natural *Bam*HI site about 24 bp downstream of the 3' end of JPI5 that was used for subcloning into the expression vector. Recombinant molecule pλP$_R$-nfSPI3$_{1179}$ was produced by digesting nfSPI3$_{1225}$-containing PCR product with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P$_R$/T^2*ori*/S10HIS-RSET-A9, as described in Section A above, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified.

Recombinant molecule pλP$_R$-nfSPI3$_{1179}$ was transformed into *E. coli* strain HB101 competent cells (available from Gibco/BRL) to form recombinant cell *E.coli*:pλP$_R$-nfSPI3$_{1179}$ using standard techniques as disclosed in Sambrook, et al., *ibid.*

C. Recombinant molecule pλP$_R$-nfSPI4$_{1140}$, containing a portion of a flea serine protease inhibitor molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1186-nucleotide DNA fragment containing nucleotides spanning from about 8 through about 1186 of SEQ ID NO:19, denoted herein as nfSPI4$_{1186}$, was PCR amplified from nucleic acid molecule nfSPI4$_{1414}$, produced as described in Example 3, using sense primer JPI5 (SEQ ID NO:37), and antisense primer was JPI17, having the nucleic acid sequence 5' CGG **AAT TCT** TTT ATT CAG TTG TTG G 3' (*Eco*RI site in bold), denoted SEQ ID NO:40. The

amplified gene sequence contained a natural *Bam*HI site about 24 bp downstream of the 3' end of JPI5 that was used for subcloning into the expression vector. Recombinant molecule pλP_R-nfSPI4$_{1140}$ was produced by digesting nfSPI4$_{1186}$-containing PCR product with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, as described in Section A above, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified.

Recombinant molecule pλP_R-nfSPI4$_{1140}$ was transformed into *E. coli* strain HB101 competent cells (available from Gibco/BRL) to form recombinant cell *E.coli*:pλP_R-nfSPI4$_{1140}$ using standard techniques as disclosed in Sambrook, et al., *ibid.*

D. Recombinant molecule pλP_R-nfSPI5$_{1140}$, containing a portion of a flea serine protease inhibitor molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1186-nucleotide DNA fragment containing nucleotides spanning from about 24 through about 1202 of SEQ ID NO:25, denoted herein as nfSPI5$_{1186}$, was PCR amplified from nucleic acid molecule nfSPI5$_{1492}$, produced as described in Example 3, using sense primer JPI5 (SEQ ID NO:37), and antisense primer was JPI17 (SEQ ID NO:40). The amplified gene sequence contained a natural *Bam*HI site about 24 bp downstream of the 3' end of JPI5 that was used for subcloning into the expression vector. Recombinant molecule pλP_R-nfSPI5$_{1140}$ was produced by digesting nfSPI5$_{1186}$-containing PCR product with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, as described in Section A above, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified.

Recombinant molecule pλP_R-nfSPI5$_{1140}$ was transformed into *E. coli* strain HB101 competent cells (available from Gibco/BRL) to form recombinant cell *E.coli*:pλP_R-nfSPI5$_{1140}$ using standard techniques as disclosed in Sambrook, et al., *ibid.*

E. Recombinant molecule pλP_R-nfSPI6$_{1136}$, containing a portion of a flea serine protease inhibitor molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment

comprising 6 histidines was produced as follows. An about 1182-nucleotide DNA fragment containing nucleotides spanning from about 38 through about 1214 of SEQ ID NO:31, denoted herein as $nfSPI6_{1182}$, was PCR amplified from nucleic acid molecule $nfSPI6_{1454}$, produced as described in Example 3, using sense primer JPI5 (SEQ ID NO:37), and antisense primer was JPI16, having the nucleic acid sequence 5' CGG **AAT TC**A TAG AGT TTG AAC TC 3' (*Eco*RI site in bold), denoted SEQ ID NO:41. The amplified gene sequence contained a natural *Bam*HI site about 24 bp downstream of the 3' end of JPI5 that was used for subcloning into the expression vector. Recombinant molecule $p\lambda P_R$-$nfSPI6_{1136}$ was produced by digesting $nfSPI6_{1182}$-containing PCR product with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, as described in Section A above, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified.

Recombinant molecule $p\lambda P_R$-$nfSPI6_{1136}$ was transformed into *E. coli* strain HB101 competent cells (available from BRL) to form recombinant cell *E.coli*:$p\lambda P_R$-$nfSPI6_{1136}$ using standard techniques as disclosed in Sambrook, et al., *ibid.*

Example 6

This Example describes the production in bacteria of several flea serine protease inhibitor proteins of the present invention.

Recombinant cells *E.coli*:$p\lambda P_R$-$nfSPI2_{1139}$, *E.coli*:$p\lambda P_R$-$nfSPI3_{1179}$, *E.coli*:$p\lambda P_R$-$nfSPI4_{1140}$, and *E.coli*:$p\lambda P_R$-$nfSPI6_{1136}$, produced as described in Example 5, were cultured in shake flasks containing an enriched bacterial growth medium containing 0.1 mg/ml ampicillin and 0.1% glucose at about 32°C. When the cells reached an OD_{600} of about 0.4 to about 0.5, expression of flea $p\lambda P_R$-$nfSPI2_{1139}$, $p\lambda P_R$-$nfSPI3_{1179}$, $p\lambda P_R$-$nfSPI4_{1140}$, and $p\lambda P_R$-$nfSPI6_{1136}$, was induced by elevating the temperature to 42°C, and culturing the cells for about 3 hours. Protein production was monitored by SDS-PAGE of recombinant cell lysates, followed by Coomassie Blue staining and immunoblot analyses using a T7 Tag monoclonal antibody (available from Novagen, Inc.). Recombinant cells *E.coli*:$p\lambda P_R$-$nfSPI2_{1139}$, *E.coli*:$p\lambda P_R$-$nfSPI3_{1179}$, *E.coli*:$p\lambda P_R$-$nfSPI4_{1140}$, and *E.coli*:$p\lambda P_R$-$nfSPI6_{1136}$ produced fusion proteins, denoted herein as PHis-

$PfSPI2_{376}$, PHis-$PfSPI3_{390}$, PHis-$PfSPI4_{376}$, and PHis-$PfSPI6_{376}$, that migrated with an apparent molecular weights of about 45 to 50 kD as predicted.

Example 7

This example describes analysis of the variable and constant domains of the nucleic acid molecules of the present invention.

The sequences of each of the flea serine protease inhibitor cDNA molecules $nfSPI1_{1584}$, $nfSPI2_{1358}$, $nfSPI3_{1838}$, $nfSPI4_{1414}$, $nfSPI5_{1492}$, and $nfSPI6_{1454}$, presented in Example 4, were subdivided into three domains based on comparisons between the six sequences. The observed versions of the three domains are summarized in Table 1. Domain I, spanning from about nucleotide 1 to about nucleotide 142 in $nfSPI1_{1584}$, from about nucleotide 1 to about nucleotide 14 in $nfSPI2_{1358}$, from about nucleotide 1 to about nucleotide 339 in $nfSPI3_{1838}$, not present in $nfSPI4_{1414}$, from about nucleotide 1 to about nucleotide 12 in $nfSPI5_{1492}$, and from about nucleotide 1 to about nucleotide 26 in $nfSPI6_{1454}$, contains upstream untranslated sequences and the coding regions for the amino termini of the serine protease inhibitor proteins. Domain II, spanning from about nucleotide 143 to about nucleotide 1195 in $nfSPI1_{1584}$, from about nucleotide 15 to about nucleotide 1067 in $nfSPI2_{1358}$, from about nucleotide 340 to about nucleotide 1392 in $nfSPI3_{1838}$, from about nucleotide 1 to about nucleotide 1049 in $nfSPI4_{1414}$, from about nucleotide 13 to about nucleotide 1065 in $nfSPI5_{1492}$, and from about nucleotide 27 to about nucleotide 1079 in $nfSPI6_{1454}$, consists of the central core of the coding sequence and encodes 350 amino acids that are extremely highly conserved (i.e. less than approximately 2% variation) between the six serine protease inhibitor clones. The predicted mature N-terminus of the serine protease inhibitors is within Domain II; thus, the variability of Domain I should have no effect on the sequence of mature serine protease inhibitor polypeptides. Domain III sequences are highly variable, yet still related to one another; Domain III, spanning from about nucleotide 1196 to about nucleotide 1584 in $nfSPI1_{1584}$, from about nucleotide 1068 to about nucleotide 1358 in $nfSPI2_{1358}$, from about nucleotide 1393 to about nucleotide 1838 in $nfSPI3_{1838}$, from about nucleotide 1050 to about nucleotide 1414 in $nfSPI4_{1414}$, from about nucleotide 1066 to about nucleotide 1492 in $nfSPI5_{1492}$, and from about nucleotide 1080 to about

nucleotide 1454 in $nfSPI6_{1454}$, encodes the C-termini of the serine protease inhibitor proteins.

While not being bound by theory, the most probable explanation for the mixing of the domain versions within the six clones sequenced is a mechanism of alternative mRNA splicing. Such a pattern was described previously by Jiang et al., 1994, *J. Biol. Chem. 269*, 55-58 for serpins in *Manduca sexta*. For this family of serpins, eight exons encode a 336-amino acid constant region, followed by a 40-45-amino acid variable region that is encoded by the ninth exon. At least twelve alternative forms of the ninth exon are tandemly arranged in the genome between exons 8 and 10. Thus, mutually exclusive exon use can account for the variability the authors observed in cDNA clones.

Based on analogy to the *Manduca* system, flea serine protease inhibitors probably exhibit a similar gene structure in that the C-terminal variable region (Domain III) is encoded by multiple exons that are used in a mutually exclusive splicing mechanism. The flea serine protease inhibitor molecules appear to differ from *Manduca* in that for the flea molecules there are at least two alternative exons at the 5' end of the gene (Domain I) as well, and there does not appear to be final constant exon (exon 10 in *Manduca*) at the 3' end. It is probable that other versions of Domain III are present in the flea genome that were not observed in the six cDNA sequences presented herein.

Table 1. Summary of sequence variations of the three domains of flea serine protease inhibitor cDNA clones. Letters represent widely divergent sequences (e.g., A vs. B); numbers denote minor variations (i.e., less than 2%) between lettered sequences (e.g., K1 vs. K2).

Clone	Domain I	Domain II	Domain III
$nfSe1_{1584}$	A	K1	W1
$nfSe2_{1358}$	B	K2	X
$nfSe3_{1838}$	B	K2	Y
$nfSe4_{1414}$	missing	K2	Z
$nfSe5_{1492}$	B	K3	Z
$nfSe6_{1454}$	A	K2	W2

Example 8

This example describes the sequencing of several flea serine protease inhibitor variable domain nucleic acid molecules.

Nucleic acid molecules encoding serine protease inhibitor variable domains were identified as follows. Two primers were designed based on the 3' end of the constant domain sequence of $nfSPI4_{1414}$, referred to herein as primer 5' new BsaI or primer 5' new HincII. Each primer was designed so that, when used in conjunction with an antisense vector primer, a properly amplified fragment of a flea serine protease inhibitor gene would include a domain corresponding to the most variable domain of serine protease inhibitor genes. Primer 5' new BsaI has nucleic acid sequence 5' CAA AAC **TGG TCT** **CCC** CGC TC 3' (*Bsa*I site in bold), represented herein as SEQ ID NO:42; and primer 5' new HincII has nucleic acid sequence 5' ATT ACA AAA **TGT TGA** CTT GC 3' (*Hinc*II site in bold), represented herein as SEQ ID NO:43. Primer 5' new *Bsa*I and primer 5' new *Hinc*II were each used separately in combination with the vector specific primer T7 having nucleic acid sequence 5' TAA TAC GAC TCA CTA TAG GG 3', represented herein as SEQ ID NO:44.

The two primer pairs were used to amplify nucleic acid molecules using standard PCR amplification conditions (e.g., Sambrook et al., *ibid.*) from a variety of cDNA libraries representing different *C. felis* developmental stages. The cDNA libraries were produced as follows. The pre-pupal cDNA library was produced as described above in Example 3. A flea mixed instar cDNA library was produced using unfed 1st instar, bovine blood-fed 1st instar, bovine blood-fed 2nd instar and bovine blood-fed 3rd instar flea larvae (this combination of tissues is referred to herein as mixed instar larval tissues for purposes of this example). Total RNA was extracted from mixed instar using the method described above using about 5,164 mixed instar larvae. Poly A+ selected RNA was isolated as described above and about 6.34 μg of mixed instar poly A+ RNA was used to construct a mixed instar cDNA expression library in lambda Uni-ZAP™XR vector (available from Stratagene), using Stratagene's ZAP-cDNA Synthesis Kit® protocol. The resultant mixed instar library was amplified to a titer of about 2.17 x 10^{10} pfu/ml with about 97% recombinants. An unfed whole adult flea cDNA library was

produced by the standard method generally described in Example 8 of related PCT Publication No. WO 96/11706.

A bovine blood-fed flea gut cDNA library was produced as follows. Total RNA was extracted from approximately 3500 guts from bovine blood-fed fleas using a standard guanidinium thiocyanate procedure for lysis and denaturation of the gut tissue, followed by centrifugation in cesium chloride to pellet the RNA. Messenger RNA was isolated from the total RNA using a Fast Track™ Kit (available from InVitrogen, San Diego, CA). A bovine blood-fed flea gut cDNA expression library was constructed in lambda Uni-ZAP™XR vector (available from Stratagene), using Stratagene's ZAP-cDNA Synthesis Kit® protocol

PCR products using the different cDNA libraries were each gel purified and cloned into the TA Vector™ (available from InVitrogen). The nucleic acid molecule was subjected to nucleic acid sequencing using the Sanger dideoxy chain termination method, as described in Sambrook et al., *ibid.*

A. A first flea serine protease inhibitor variable domain nucleic acid molecule isolated from the mixed instar cDNA library was determined to comprise nucleic acid molecule $nfSPI7_{549}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:45. Translation of SEQ ID NO:45 suggests that nucleic acid molecule $nfSPI7_{549}$ encodes a portion of a serine protease inhibitor protein of about 134 amino acids, referred to herein as $PfSPI7_{134}$, having amino acid sequence SEQ ID NO:46, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:45 and the last codon spans from nucleotide 402 through nucleotide 404 of SEQ ID NO:45. The complement of SEQ ID NO:45 is represented herein by SEQ ID NO:47. Comparison of amino acid sequence SEQ ID NO:46 (i.e., the amino acid sequence of $PfSPI7_{134}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:46, showed the most homology, i.e., about 34% identity, between SEQ ID NO:46 and *Mus musculus* antithrombin III precursor protein. Comparison of nucleic acid sequence SEQ ID NO:45 (i.e., the nucleic acid sequence of $nfSPI7_{549}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:45, showed the most homology, i.e., about 38% identity, between SEQ ID NO:45 and human bomapin gene.

B. A second flea serine protease inhibitor variable domain nucleic acid molecule isolated from the mixed instar cDNA library was determined to comprise nucleic acid molecule $nfSPI8_{549}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:48. Translation of SEQ ID NO:48 suggests that nucleic acid molecule $nfSPI8_{549}$ encodes a serine protease inhibitor variable domain protein of about 149 amino acids, referred to herein as $PfSPI8_{149}$, having amino acid sequence SEQ ID NO:49, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:48 and the last codon spans from nucleotide 447 through nucleotide 449 of SEQ ID NO:48. The complement of SEQ ID NO:48 is represented herein by SEQ ID NO:50. Comparison of amino acid sequence SEQ ID NO:49 (i.e., the amino acid sequence of $PfSPI8_{149}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:49, showed the most homology, i.e., about 36% identity, between SEQ ID NO:49 and human bomapin precursor protein. Comparison of nucleic acid sequence SEQ ID NO:48 (i.e., the nucleic acid sequence of $nfSPI8_{549}$) with nucleic acid sequences reported in GeEmbl indicates that SEQ ID NO:48, showed the most homology, i.e., about 41% identity, between SEQ ID NO:48 and human bomapin gene.

C. A third flea serine protease inhibitor variable domain nucleic acid molecule isolated from the bovine blood-fed gut cDNA library was determined to comprise nucleic acid molecule $nfSPI9_{581}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:51. Translation of SEQ ID NO:51 suggests that nucleic acid molecule $nfSPI9_{581}$ encodes a serine protease inhibitor variable domain protein of about 136 amino acids, referred to herein as $PfSPI9_{136}$, having amino acid sequence SEQ ID NO:52, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:51 and the last codon spans from nucleotide 408 through nucleotide 410 of SEQ ID NO:51. The complement of SEQ ID NO:51 is represented herein by SEQ ID NO:53. Comparison of amino acid sequence SEQ ID NO:52 (i.e., the amino acid sequence of $PfSPI9_{136}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:52, showed the most homology, i.e., about 45% identity, between SEQ ID NO:52 and *Bombyx mori* anti-trypsin precusor protein. Comparison of nucleic acid sequence SEQ ID NO:51 (i.e., the nucleic acid sequence of $nfSPI9_{581}$) with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:51, showed the

most homology, i.e., about 52% identity, between SEQ ID NO:51 and *Bombyx mori* anti-trypsin gene.

D. A fourth flea serine protease inhibitor variable domain nucleic acid molecule isolated from the flea pre-pupal cDNA library was determined to comprise nucleic acid molecule nfSPI10$_{654}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:54. Translation of SEQ ID NO:54 suggests that nucleic acid molecule nfSPI10$_{654}$ encodes a serine protease inhibitor variable domain protein of about 118 amino acids, referred to herein as PfSPI10$_{118}$, having amino acid sequence SEQ ID NO:55, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:54 and the last codon spans from nucleotide 354 through nucleotide 356 of SEQ ID NO:54. The complement of SEQ ID NO:54 is represented herein by SEQ ID NO:56. Comparison of amino acid sequence SEQ ID NO:55 (i.e., the amino acid sequence of PfSPI10$_{118}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:55, showed the most homology, i.e., about 38% identity, between SEQ ID NO:55 and *Manduca sexta* alaserpin precursor protein. Comparison of nucleic acid sequence SEQ ID NO:54 (i.e., the nucleic acid sequence of nfSPI10$_{654}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:54, showed the most homology, i.e., about 41% identity, between SEQ ID NO:54 and human bomapin gene.

E. A fifth flea serine protease inhibitor variable domain nucleic acid molecule isolated from the flea pre-pupal cDNA library was determined to comprise nucleic acid molecule nfSPI11$_{670}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:57. Translation of SEQ ID NO:57 suggests that nucleic acid molecule nfSPI11$_{670}$ encodes a serine protease inhibitor variable domain protein of about 125 amino acids, referred to herein as PfSPI11$_{125}$, having amino acid sequence SEQ ID NO:58, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:57 and the last codon spans from nucleotide 375 through nucleotide 377 of SEQ ID NO:57. The complement of SEQ ID NO:57 is represented herein by SEQ ID NO:59. Comparison of amino acid sequence SEQ ID NO:58 (i.e., the amino acid sequence of PfSPI11$_{125}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:58, showed the most homology, i.e., about 43% identity, between SEQ ID NO:58 and *Manduca sexta* alaserpin precursor protein. Comparison of nucleic acid

sequence SEQ ID NO:57 (i.e., the nucleic acid sequence of nfSPI11$_{670}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:57, showed the most homology, i.e., about 40% identity, between SEQ ID NO:57 and human bomapin gene.

F. A sixth flea serine protease inhibitor variable domain nucleic acid molecule isolated from the unfed whole adult flea cDNA library was determined to comprise nucleic acid molecule nfSPI12$_{706}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:60. Translation of SEQ ID NO:60 suggests that nucleic acid molecule nfSPI12$_{706}$ encodes a serine protease inhibitor variable domain protein of about 136 amino acids, referred to herein as PfSPI12$_{136}$, having amino acid sequence SEQ ID NO:61, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:60 and the last codon spans from nucleotide 408 through nucleotide 410 of SEQ ID NO:60. The complement of SEQ ID NO:60 is represented herein by SEQ ID NO:62. Comparison of amino acid sequence SEQ ID NO:61 (i.e., the amino acid sequence of PfSPI12$_{136}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:61, showed the most homology, i.e., about 45% identity, between SEQ ID NO:61 and *Manduca sexta* alaserpin precursor protein protein. Comparison of nucleic acid sequence SEQ ID NO:60 (i.e., the nucleic acid sequence of nfSPI12$_{706}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:60, showed the most homology, i.e., about 38% identity, between SEQ ID NO:60 and human bomapin gene.

G. A seventh flea serine protease inhibitor variable domain nucleic acid molecule isolated from the flea pre-pupal cDNA library was determined to comprise nucleic acid molecule nfSPI13$_{623}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:63. Translation of SEQ ID NO:63 suggests that nucleic acid molecule nfSPI13$_{623}$ encodes a serine protease inhibitor variable domain protein of about 122 amino acids, referred to herein as PfSPI13$_{122}$, having amino acid sequence SEQ ID NO:64, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:63 and the last codon spans from nucleotide 366 through nucleotide 368 of SEQ ID NO:63. The complement of SEQ ID NO:63 is represented herein by SEQ ID NO:65. Comparison of amino acid sequence SEQ ID NO:64 (i.e., the amino acid sequence of PfSPI13$_{122}$) with amino acid sequences reported in SwissProt indicates that

SEQ ID NO:64, showed the most homology, i.e., about 39% identity, between SEQ ID NO:64 and human leukocyte esterase inhibitor protein. Comparison of nucleic acid sequence SEQ ID NO:63 (i.e., the nucleic acid sequence of $nfSPI13_{623}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:63, showed the most homology, i.e., about 37% identity, between SEQ ID NO:63 and human bomapin gene.

H. A eighth flea serine protease inhibitor variable domain nucleic acid molecule isolated from the bovine blood-fed flea gut cDNA library was determined to comprise nucleic acid molecule $nfSPI14_{731}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:66. Translation of SEQ ID NO:66 suggests that nucleic acid molecule $nfSPI14_{731}$ encodes a serine protease inhibitor variable domain protein of about 137 amino acids, referred to herein as $PfSPI14_{137}$, having amino acid sequence SEQ ID NO:67, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:66 and the last codon spans from nucleotide 411 through nucleotide 413 of SEQ ID NO:66. The complement of SEQ ID NO:66 is represented herein by SEQ ID NO:68. Comparison of amino acid sequence SEQ ID NO:67 (i.e., the amino acid sequence of $PfSPI14_{137}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:67, showed the most homology, i.e., about 40% identity, between SEQ ID NO:67 and *Equus callabus* esterase inhibitor protein. Comparison of nucleic acid sequence SEQ ID NO:66 (i.e., the nucleic acid sequence of $nfSPI14_{731}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:66, showed the most homology, i.e., about 38% identity, between SEQ ID NO:66 and human bomapin gene.

I. A ninth flea serine protease inhibitor variable domain nucleic acid molecule isolated from the unfed whole adult flea cDNA library was determined to comprise nucleic acid molecule $nfSPI15_{685}$, the nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:69. Translation of SEQ ID NO:69 suggests that nucleic acid molecule $nfSPI15_{685}$ encodes a serine protease inhibitor variable domain protein of about 135 amino acids, referred to herein as $PfSPI15_{135}$, having amino acid sequence SEQ ID NO:70, assuming the first codon spans from nucleotide 3 through nucleotide 5 of SEQ ID NO:69 and the last codon spans from nucleotide 405 through nucleotide 407 of SEQ ID NO:69. The complement of SEQ ID

NO:69 is represented herein by SEQ ID NO:71. Comparison of amino acid sequence SEQ ID NO:70 (i.e., the amino acid sequence of PfSPI15$_{135}$) with amino acid sequences reported in SwissProt indicates that SEQ ID NO:70, showed the most homology, i.e., about 48% identity, between SEQ ID NO:70 and *Bombyx mori* antichymotrypsin II protein. Comparison of nucleic acid sequence SEQ ID NO:69 (i.e., the nucleic acid sequence of nfSPI15$_{685}$) with nucleic acid sequences reported in GenEmbl indicates that SEQ ID NO:69, showed the most homology, i.e., about 38% identity, between SEQ ID NO:69 and human antithrombin III variant gene.

Example 9

This example discloses the production of a several recombinant cells of the present invention using serine protease inhibitor variable domain nucleic acid molecules of the present invention.

Each of nucleic acid molecules nfSPI7$_{549}$, nfSPI8$_{549}$, nfSPI9$_{581}$, nfSPI10$_{654}$, nfSPI12$_{706}$, nfSPI13$_{623}$ and nfSPI15$_{685}$, were digested with either the restriction enzymes *Hinc*II and *Xho*I, or *Bsa*I and *Xho*I. The resulting *Hinc*II and *Xho*I, or *Bsa*I and *Xho*I digested fragments were ligated to a portion of DNA that had been isolated from nfSPI4$_{1414}$ digested with *Bam*HI and *Hinc*II, or *Bam*HI and *Bsa*I. The nfSPI4$_{1414}$ *Bam*HI and *Hinc*II fragment, or nfSPI4$_{1414}$ *Bam*HI and *Bsa*I fragment, encoded the majority of the constant domain of nfSPI4$_{1414}$. The resulting ligation products that include chimeric serine protease inhibitor open reading frames, are referred to herein as nfSPIC4:V7, nfSPIC4:V8, nfSPIC4:V9, nfSPIC4:V10, nfSPIC4:V12, nfSPIC4:V13 and nfSPIC4:V15, respectively. The nfSPIC4:V7, nfSPIC4:V9, nfSPIC4:V10 or nfSPIC4:V12 ligation products were then digested with the restriction enzymes *Bam*HI and *Xho*I and separately ligated into pBluescript vector which had been digested with the same restriction enzymes. The resulting ligation products are referred to herein as pBluSPI:C4:V7, pBluSPI:C4:V9, pBluSPI:C4:V10 and pBluSPI:C4:V12, respectively.

A. Recombinant molecule pλP$_R$-nfSPIC4:V7$_{1168}$, containing a chimeric serine protease inhibitor open reading frame molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1168-nucleotide DNA fragment denoted herein as nfSPIC4:V7$_{1168}$ containing nucleotides

spanning from 1 through 761 of $nfSPI4_{1414}$ ligated to nucleotides spanning from 1 through 407 of $nfSPI7_{549}$, was PCR amplified from nucleic acid molecule pBluSPI:C4:V7, using sense primer T-3pBS, having the nucleic acid sequence 5' ATT AAC CCT CAC TAA AG 3' (SEQ ID NO:83), and antisense primer, Srp73'end, having nucleic acid sequence 5' GCG **GAA TTC** TTA AGG ATT AAC GTG TTG AAC 3' and denoted herein as SEQ ID NO:93 (*Eco*RI site shown in bold). The amplified gene sequence contained a natural *Bam*HI site about 100 bp downstream of the T-3pBS primer that was used for subcloning into the expression vector. Recombinant molecule $p\lambda P_R$-$nfSPIC4{:}V7_{1168}$ was produced by digesting $nfSPIC4{:}V7_{1168}$ with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, the production of which is described in PCT Publication No. US95/02941, by Tripp et al., published 9/14/95, Example 7, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified.

Recombinant molecule $p\lambda P_R$-$nfSPIC4{:}V7_{1168}$ was transformed into *E. coli* strain HB101 competent cells (available from Gibco/BRL, Gaithersburg, MD) to form recombinant cell *E.coli*:$p\lambda P_R$-$nfSPIC4{:}V7_{1168}$ using standard techniques as disclosed in Sambrook, et al., *ibid.*

B. Recombinant molecule $p\lambda P_R$-$nfSPIC4{:}V9_{1174}$, was produced using the methods described above in section 9(A) except the antisense primer used to produce a PCR product from pBluSPI:C4:V9 was Srp93'end, having nucleic acid sequence 5' GGA **ATT C**TT ATT GCA CAA ATC ATC C 3' and denoted herein as SEQ ID NO:94 (*Eco*RI site shown in bold). An about 1174-nucleotide DNA fragment denoted herein as $nfSPIC4{:}V9_{1174}$ containing nucleotides spanning from 1 through 794 of $nfSPI4_{1414}$ and nucleotides spanning from 22 through 413 of SEQ ID NO:51, was PCR amplified from nucleic acid molecule pBluSPI:C4:V9 produced as described in section 9. Recombinant molecule $p\lambda P_R$-$nfSPIC4{:}V9_{1174}$ was produced by digesting $nfSPIC4{:}V9_{1174}$ with *Bam*HI and *Eco*RI restriction endonucleases, gel purifying the resulting fragment and subcloning the fragment into the expression vector P_R/T^2*ori*/S10HIS-RSET-A9, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified, to produce the recombinant molecule $p\lambda P_R$-$nfSPIC4{:}V9_{1174}$.

Recombinant molecule pλP_R-nfSPIC4:V9_{1174} was transformed into *E. coli* strain HB101 competent cells to form recombinant cell *E.coli*:pλP_R-nfSPIC4:V9_{1174} using methods described in Section 9(A).

C. Recombinant molecule pλP_R-nfSPIC4:V10_{1159}, was produced using the methods described above in section 9(A) except the antisense primer used to produce a PCR product from pBluSPI:C4:V10 was Srp103'end, having nucleic acid sequence 5' GCG **GAA TTC** AAC AAA AGT GTG TTC 3' and denoted herein as SEQ ID NO:87 (*Eco*RI site shown in bold) and the sense primer used was the T-3pBS primer (SEQ ID NO:83). An about 1159-nucleotide DNA fragment denoted herein as nfSPIC4:V10_{1159} containing nucleotides spanning from 1 through 803 of nfSPI4_{1414} and nucleotides spanning from 1 through 356 of SEQ ID NO:54, was PCR amplified from nucleic acid molecule pBluSPI:C4:V10 produced as described in section 9. Recombinant molecule pλP_R-nfSPIC4:V10_{1159} was produced by digesting nfSPIC4:V10_{1159} with *Bam*HI and *Eco*RI restriction endonucleases, gel purifying the resulting fragment and subcloning the fragment into the expression vector P_R/T^2*ori*/S10HIS-RSET-A9, which had been similarly cleaved with *Bam*HI and *Eco*RI and gel purified, to produce the recombinant molecule pλP_R-nfSPIC4:V10_{1159}.

Recombinant molecule pλP_R-nfSPIC4:V10_{1159} was transformed into *E. coli* strain HB101 competent cells to form recombinant cell *E.coli*:pλP_R-nfSPIC4:V10_{1159} using methods described in Section 9(A).

D. Recombinant molecule pλP_R-nfSPIC4:V8_{1222}, containing a chimeric serine protease inhibitor open reading frame molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1222 nucleotide DNA fragment denoted herein as nfSPIC4:V8_{1222} containing nucleotides spanning from 1 to 794 of nfSPI4_{1414} ligated to nucleotides spanning from 22 through 449 of nfSPI8_{549} was PCR amplified from nucleic acid molecule nfSPIC4:V8 using sense primer serpin5' end having nucleic acid sequence 5' ATA **GGA TCC** CCA GGA ATT GTC 3' (SEQ ID NO 84; *Bam*H1 site in bold), and antisense primer, Srp8 3'end, having nucleic acid sequence 5' GCG **AGA TCT** CTA GTT ATT AAT ATT GGT TAA 3' and denoted herein as SEQ ID NO:85 (*Bgl*II site shown in bold). Recombinant

molecule pλP_R-nfSPIC4:V8 was produced by digesting nfSPIC4:V8_{1222} with *Bam*HI and *Bgl*II restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, which had been similarly cleaved with *Bam*HI and *Bgl*II and gel purified, to produce the recombinant molecule pλP_R-nfSPIC4:V8_{1222}.

Recombinant molecule pλP_R-nfSPIC4:V8_{1222} was transformed into *E. coli* strain HB101 competent cells to form recombinant cell *E.coli*:pλP_R-nfSPIC4:V8_{1222} using methods described in Section 9(A).

E. Recombinant molecule pλP_R-nfSPIC4:V15_{1179}, containing a chimeric serine protease inhibitor open reading frame molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1179 nucleotide DNA fragment denoted herein as nfSPIC4:V15_{1179} containing nucleotides spanning from 1 to 794 of nfSPI4_{1414} ligated to nucleotides spanning from 22 through 449 of nfSPI15_{685} was PCR amplified from nucleic acid molecule nfSPIC4:V15 using the sense primer serpin5'end (SEQ ID NO:84) and the antisense primer, Srp15 3', having nucleic acid sequence 5' GCG**GAATTC**TCATGGTGACTGAACGCG 3' (denoted herein as SEQ ID NO:86; *Eco*R1 site shown in bold). Recombinant molecule pλP_R-nfSPIC4:V15_{1179} was produced by digesting nfSPIC4:V15_{1179} with *Bam*HI and *Eco*R1 restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, which had been similarly cleaved with *Bam*HI and *Eco*R1 and gel purified, to produce the recombinant molecule pλP_R-nfSPIC4:V15_{1179}.

Recombinant molecule pλP_R-nfSPIC4:V15_{1179} was transformed into *E. coli* strain HB101 competent cells to form recombinant cell *E.coli*:pλP_R-nfSPIC4:V15_{1179} using methods described in Section 9(A).

F. Recombinant molecule pλP_R-nfSPIC4:V12_{1171}, containing a chimeric serine protease inhibitor open reading frame molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1171 nucleotide DNA fragment denoted herein as nfSPIC4:V12_{1171} containing

nucleotides spanning from 1 to 761 of $nfSPI4_{1414}$ ligated to nucleotides spanning from 1 through 410 of $nfSPI12_{706}$ was PCR amplified from nucleic acid molecule pBluSPIC4:V12 using sense primer T-3pBS (SEQ ID NO:83), and antisense primer, Srp123'end, having nucleic acid sequence 5' GCG **GAA TTC** TTA TTT GGG AGA TAT AAC TCG 3' and denoted herein as SEQ ID NO:91 (*Eco*R1 site shown in bold). Recombinant molecule pλP_R-nfSPIC4:$V12_{1171}$ was produced by digesting nfSPIC4:$V12_{1171}$ with *Bam*HI and *Eco*R1 restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, which had been similarly cleaved with *Bam*HI and *Eco*R1 and gel purified, to produce the recombinant molecule pλP_R-nfSPIC4:$V12_{1171}$.

Recombinant molecule pλP_R-nfSPIC4:$V12_{1171}$ was transformed into *E. coli* strain HB101 competent cells to form recombinant cell *E.coli*:pλP_R-nfSPIC4:$V12_{1171}$ using methods described in Section 9(A).

G. Recombinant molecule pλP_R-nfSPIC4:$V13_{1171}$, containing a chimeric serine protease inhibitor open reading frame molecule operatively linked to bacteriophage lambda transcription control sequences and to a fusion sequence encoding a poly-histidine segment comprising 6 histidines was produced as follows. An about 1171 nucleotide DNA fragment denoted herein as nfSPIC4:$V13_{1171}$ containing nucleotides spanning from 1 to 803 of $nfSPI4_{1414}$ ligated to nucleotides spanning from 1 through 368 of $nfSPI13_{623}$ was PCR amplified from nucleic acid molecule nfSPIC4:V13 using the sense primer serpin5' end (SEQ ID NO:84), and antisense primer Srp13 3', having nucleic acid sequence 5' CGC **GAA TTC** TCA TTC GAC AAA ATG ACC 3' and denoted herein as SEQ ID NO:92 (*Eco*RI site shown in bold). Recombinant molecule pλP_R-nfSPIC4:$V13_{1171}$ was produced by digesting nfSPIC4:$V13_{1171}$ with *Bam*HI and *Eco*RI restriction endonucleases, column purifying the resulting fragment, and directionally subcloning the fragment into expression vector P_R/T^2*ori*/S10HIS-RSET-A9, which had been similarly cleaved with *Bam*HI and *Eco*R1 and gel purified, to produce the recombinant molecule pλP_R-nfSPIC4:$V13_{1171}$.

Recombinant molecule pλP_R-nfSPIC4:$V13_{1171}$ was transformed into *E. coli* strain HB101 competent cells to form recombinant cell *E.coli*:pλP_R-nfSPIC4:$V13_{1171}$ using methods described in Section 9(A).

Example 10

This Example describes the production in bacteria of several flea serine protease inhibitor proteins of the present invention.

Recombinant cells *E.coli*:pλP_R-nfSPIC4:$V7_{1168}$, *E.coli*:pλP_R-nfSPIC4:$V8_{1222}$, *E.coli*:pλP_R-nfSPIC4:$V9_{1174}$, *E.coli*:pλP_R-nfSPIC4:$V10_{1159}$, *E.coli*:pλP_R-nfSPIC4:$V12_{1171}$, *E.coli*:pλP_R-nfSPIC4:$V13_{1171}$, *E.coli*:pλP_R-nfSPIC4:$V15_{1179}$, produced as described in Example 9, were cultured in shake flasks containing an enriched bacterial growth medium containing 0.1 mg/ml ampicillin and 0.1% glucose at about 32°C. When the cells reached an OD_{600} of about 0.4 to about 0.5, expression of flea *E.coli*:pλP_R-nfSPIC4:$V7_{1168}$, *E.coli*:pλP_R-nfSPIC4:$V9_{1174}$, *E.coli*:pλP_R-nfSPIC4:$V10_{1159}$, *E.coli*:pλP_R-nfSPIC4:$V12_{1171}$, *E.coli*:pλP_R-nfSPIC4:$V13_{1171}$, *E.coli*:pλP_R-nfSPIC4:$V15_{1179}$, were each induced by elevating the temperature to 42°C, and culturing the cells for about 3 hours. Expression of flea *E.coli*:pλP_R-nfSPIC4:$V8_{1222}$ was induced by the addition of 0.5 mM isopropyl-B-D-thiogalactoside (IPTG) to the culture medium, and the cells were cultured for about 2 hours at about 32°C.

Protein production was monitored by SDS-PAGE of recombinant cell lysates and immunoblot analyses using a T7 Tag monoclonal antibody (available from Novagen, Inc.) and the anti-SPI2 polyclonal antiserum (described in detail in Example 5). Recombinant cells *E.coli*:pλP_R-nfSPIC4:$V7_{1168}$, *E.coli*:pλP_R-nfSPIC4:$V9_{1174}$ and *E.coli*:pλP_R-nfSPIC4:$V15_{1179}$ produced fusion proteins, denoted herein as PHis-PfSPIC4:V7, PHis-PfSPIC4:V9 and PHis-PfSPIC4:V15 that migrated with an apparent molecular weight of about 45 kD as predicted. Recombinant cells *E.coli*:pλP_R-nfSPIC4:$V10_{1159}$ produced the fusion protein denoted herein as PHis-PfSPIC4:V10 that migrated with an apparent molecular weight of about 44 kD as predicted. Recombinant cells *E.coli*:pλP_R-nfSPIC4:$V8_{1222}$ produced the fusion protein denoted herein as PHis-PfSPIC4:V8 that migrated with an apparent molecular weight of about 51 kD as predicted. Recombinant cells *E.coli*:pλP_R-nfSPIC4:$V12_{1171}$ and *E.coli*:pλP_R-nfSPIC4:$V13_{1171}$ produced the fusion protein denoted herein as PHis-PfSPIC4:V12 and PHis-PfSPIC4:V13, respectively, each of which migrated with an apparent molecular weight of about 49 kD as predicted.

Example 11

This example demonstrates the production of a serine protease inhibitor protein of the present invention in eukaryotic cells.

A. Recombinant molecule pBv-nfSPI3$_{1222}$, containing a flea serine protease inhibitor nucleic acid molecule spanning nucleotides from about 325 through about 1546 of SEQ ID NO:13, operatively linked to baculovirus polyhedron transcription control sequences were produced in the following manner. A PCR fragment of 1222 nucleotides, herein denoted nfSPI3$_{1222}$, having SEQ ID NO:72 was amplified from nfSPI3$_{1838}$ using the sense primer Serpin3For, having the nucleic acid sequence 5'- GGA **AGA TCT** ATA AAT ATG CCG CGT CCT CAG TTT G -3' (SEQ ID NO:73; *Bgl*II site shown in bold) and the antisense primer Serpin3Rev, having the nucleic acid sequence 5'-CGG **AAT TCT** AAT TGG TAA ATC TCC CAG AG -3' (SEQ ID NO:74; *Eco*RI site shown in bold). A portion of the sense primer was designed from the pol h sequence of baculovirus with modifications to enhance expression in the baculovirus system.

The resulting 1222-bp PCR product (referred to as Bv-nfSPI3$_{1222}$) was digested with *Bgl*II and *Eco*RI restriction endonucleases and subcloned into unique *Bgl*II and *Eco*RI sites of pVL1392 baculovirus shuttle plasmid (available from Pharmingen, San Diego, CA) to produce the recombinant molecule referred to herein as pVL-nfSPI3$_{1222}$.

The resultant recombinant molecule pVL-nfSPI3$_{1222}$, was verified for proper insert orientation by restriction mapping. Such a recombinant molecule can be co-transfected with a linear Baculogold baculovirus DNA (available from Pharmingen) into *S. frugiperda* Sf9 cells (available from InVitrogen) to form the recombinant cells denoted *S. frugiperda*:pVL-nfSPI3$_{1222}$. *S. frugiperda*:pVL-nfSPI3$_{1222}$ was cultured in order to produce a flea serine protease inhibitor protein PfSPI3$_{406}$ (referred to herein as SEQ ID NO:95).

An immunoblot of supernatant from cultures of *S. frugiperda*:pVL-nfSPI3$_{1222}$ cells producing the flea serine protease inhibitor protein PfSPI3$_{406}$ was performed using the anti-SPI2 polyclonal antiserum described in detail in Example 5. Blots were incubated using serum samples from the pre-bleed or from serum collected 14 days after

the first boost of the rabbit. Analysis of the supernatent from cultures of *S. frugiperda*:pVL-nfSPI3$_{1222}$ cells identified an about 41 kD and about 46 kD proteins.

B. Recombinant molecule pBv-nfSPI6$_{1155}$, containing a flea serine protease inhibitor nucleic acid molecule spanning nucleotides from about 154 through about 1308 of SEQ ID NO:31, operatively linked to baculovirus polyhedron transcription control sequences were produced in the following manner. A PCR fragment of 1155 nucleotides, herein denoted nfSPI6$_{1155}$, having SEQ ID NO:75 was amplified from nfSPI6$_{1454}$ using the sense primer Serpin6For, having the nucleic acid sequence 5'- GGA **AGA TCT** ATA AAT ATG ATT AAC GCA CGA CTT -3' (SEQ ID NO:76; *Bgl*II site shown in bold) and the antisense primer Serpin6Rev, having the nucleic acid sequence 5'-CCG **GAA TTC** ATA GAG TTT GAA CTC GCC C -3' (SEQ ID NO:77; *Eco*RI site shown in bold). A portion of the sense primer was designed from the pol h sequence of baculovirus with modifications to enhance expression in the baculovirus system.

The resulting 1155-bp PCR product (referred to as Bv-nfSPI6$_{1155}$) was digested with *Bgl*II and *Eco*RI restriction endonucleases and subcloned into unique *Bgl*II and *Eco*RI sites of pVL1392 baculovirus shuttle plasmid to produce the recombinant molecule referred to herein as pVL-nfSPI6$_{1155}$.

The resultant recombinant molecule pVL-nfSPI6$_{1155}$, was verified for proper insert orientation by restriction mapping. Such a recombinant molecule can be co-transfected with a linear Baculogold baculovirus DNA into *S. frugiperda* Sf9 cells to form the recombinant cells denoted *S. frugiperda*:pVL-nfSPI6$_{1155}$. *S. frugiperda*:pVL-nfSPI6$_{1155}$ was cultured in order to produce a flea serine protease inhibitor protein PfSPI6$_{385}$ (referred to herein as SEQ ID NO:96).

An immunoblot of supernatant from cultures of *S. frugiperda*:pVL-nfSPI6$_{1155}$ cells producing the flea serine protease inhibitor protein PfSPI6$_{385}$ was performed using the anti-SPI2 polyclonal antiserum described in detail in Example 5. Blots were incubated using serum samples from the pre-bleed or from serum collected 14 days after the first boost of the rabbit. Analysis of the supernatent from cultures of *S. frugiperda*:pVL-nfSPI6$_{1155}$ cells identified an about 41 kD and about 45 kD proteins.

C. Recombinant molecule pBv-nfSPI2$_{1065}$, containing a flea serine protease inhibitor nucleic acid molecule spanning nucleotides from about 102 through about 1066

of SEQ ID NO:7, operatively linked to baculovirus polyhedron transcription control sequences were produced in the following manner. A PCR fragment of 1066 nucleotides, herein denoted nfSPI2$_{1065}$, having SEQ ID NO:78 was amplified from nfSPI2$_{1358}$ using the sense primer Serpin2For, having the nucleic acid sequence 5'- GCG **GAA TTC** GAT CCC CAG GAA TTG TCT ACA AGT ATT AAC C -3' (SEQ ID NO:79; *Eco*RI site shown in bold) and the antisense primer Serpin2Rev, having the nucleic acid sequence 5'- GCG **AGA TCT** TTA AAG GGA TTT AAC ACA TCC ACT GAA CAA AAC AG -3' (SEQ ID NO:80; *Bgl*II site shown in bold).

The resulting 1065-bp PCR product (referred to as Bv-nfSPI2$_{1065}$) was digested with *Bgl*II and *Eco*RI restriction endonucleases and subcloned into unique *Bgl*II and *Eco*RI sites of pAcGP67 (available from Pharmingen)s baculovirus shuttle plasmid to produce the recombinant molecule referred to herein as pAcG-nfSPI2$_{1065}$.

The resultant recombinant molecule pAcG-nfSPI2$_{1065}$, was verified for proper insert orientation by restriction mapping. Such a recombinant molecule can be co-transfected with a linear Baculogold baculovirus DNA into *S. frugiperda* Sf9 cells to form the recombinant cells denoted *S. frugiperda*:pAcG-nfSPI2$_{1065}$. *S. frugiperda*:pAcG-nfSPI2$_{1065}$ was cultured in order to produce a flea serine protease inhibitor protein PfSPI2$_{354}$ (referred to herein as SEQ ID NO:97).

An immunoblot of supernatant from cultures of *S. frugiperda*:pAcG-nfSPI2$_{1065}$ cells producing the flea serine protease inhibitor protein PfSPI2$_{355}$ was performed using the anti-SPI2 polyclonal antiserum described in detail in Example 5. Blots were incubated using serum samples from the pre-bleed or from serum collected 14 days after the first boost of the rabbit. Analysis of the supernatent from cultures of *S. frugiperda*:pAcG-nfSPI2$_{1065}$ cells identified an about 45 kD protein.

D. Recombinant molecule pBv-nfSPI4$_{1070}$, containing a flea serine protease inhibitor nucleic acid molecule spanning nucleotides from about 84 through about 1153 of SEQ ID NO:19, operatively linked to baculovirus polyhedron transcription control sequences were produced in the following manner. A PCR fragment of 1070 nucleotides, herein denoted nfSPI4$_{1070}$, having SEQ ID NO:81 was amplified from nfSPI4$_{1414}$ using the sense primer Serpin2For described above and the antisense primer

Serpin4Rev, having the nucleic acid sequence 5'- CGC **AGA TCT** TTA TTC AGT TGT TGG TTT AAC AAG ACG ACC -3' (SEQ ID NO:82; *BglII* site shown in bold).

The resulting 1070-bp PCR product (referred to as Bv-nfSPI4$_{1070}$) was digested with *BglII* and *EcoRI* restriction endonucleases and subcloned into unique *BglII* and *EcoRI* sites of pAcGP67 baculovirus shuttle plasmid to produce the recombinant molecule referred to herein as pAcG-nfSPI4$_{1070}$.

The resultant recombinant molecule pAcG-nfSPI4$_{1070}$, was verified for proper insert orientation by restriction mapping. Such a recombinant molecule can be co-transfected with a linear Baculogold baculovirus DNA into *S. frugiperda* Sf9 cells to form the recombinant cells denoted *S. frugiperda*:pAcG-nfSPI4$_{1070}$. *S. frugiperda*:pAcG-nfSPI4$_{1070}$ was cultured in order to produce a flea serine protease inhibitor protein PfSPI4$_{356}$ (referred to herein as SEQ ID NO:98).

An immunoblot of supernatant from cultures of *S. frugiperda*:pAcG-nfSPI4$_{1070}$ cells producing the flea serine protease inhibitor protein PfSPI4$_{356}$ was performed using the anti-SPI2 polyclonal antiserum described in detail in Example 5. Blots were incubated using serum samples from the pre-bleed or from serum collected 14 days after the first boost of the rabbit. Analysis of the supernatent from cultures of *S. frugiperda*:pAcG-nfSPI4$_{1070}$ cells identified an about 41 kD protein.

Example 12

This example describes the purification of serine protease inhibitor proteins from wandering larvae.

About 15,000 bovine blood-fed wandering larvae were homogenized in Tris buffered saline (TBS), pH 8 by sonication in 50 ml Oak Ridge centrifuge tubes (available from Nalgene Co., Rochester, NY) by sonicating 4 times 30 seconds each at a setting of 5 of a model W-380 Sonicator (available from Heat Systems-Ultrasonics, Inc.). The sonicates were clarified by centrifugation at 27,000 x g for 30 minutes to produce an extract. Soluble protein in the extract was removed by aspiration and diluted to a volume of about 15 ml in TBS. Sodium chloride (NaCl) was then added to the extract to bring the final concentration of NaCl to about 400 mM. The extract was then applied to a column containing about 2 ml of *p*-aminobenzamidine cross-linked to Sepharose® beads (available from Sigma, St. Louis, MO), previously equilibrated in 50

mM Tris, pH 8, 400 mM NaCl, and incubated overnight. The unbound serine protease inhibitor proteins were then drained from the column and dialyzed against 2 changes of about 1 liter of 10 mM phosphate buffer, pH 7.2, 10 mM NaCl. Two aliquots of about 9 ml each were applied to a chromatography column containing about 10 ml of Macro-Prep Ceramic Hydroxyapatite, Type I, 20 μm beads (available from Bio-Rad Laboratories, Hercules, CA), previously equilibrated with 10 mM phosphate buffer, pH 7.2 containing 10 mM NaCl. The column was washed with 10 mM phosphate buffer, pH 7.2 containing 10 mM NaCl until all unbound protein was removed. Protein bound to the column was then eluted with a linear gradient from 10 mM phosphate buffer, pH 7.2 containing 10 mM NaCl to 0.5 M phosphate buffer, pH 6.5 containing 10 mM NaCl. Fractions were assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the rabbit anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that serine protease inhibitor proteins were eluted at about 120 mM phosphate.

The fractions that contained the most serine protease inhibitor proteins were combined and diafiltered into about 25 ml of 25 mM Tris (pH 8), 10 mM NaCl, in preparation for anion exchange chromatography. The sample was then applied to a Uno Q6 anion exchange column (available from Bio-Rad). The column was washed with 25 mM Tris (pH 8), 10 mM NaCl until all unbound protein was removed. Protein bound to the column was then eluted with a linear gradient from 10 mM to 1 M NaCl in 25 mM Tris, pH 8. Fractions were assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that the serine protease inhibitor proteins were eluted at about 260 mM NaCl.

Fractions containing the most serine protease inhibitor proteins were pooled and diafiltered into a total volume of about 6 ml of 20 mM MES buffer (2-(N-morpholino)ethanesulfonic acid), pH 6, containing 10 mM NaCl, in preparation for cation exchange chromatography. The sample was then applied to an Uno S1 cation exchange column (available from Bio-Rad) equilibrated in MES buffer containing 10 mM NaCl. The column was washed with MES buffer containing 10 mM NaCl until all unbound protein was removed. Protein bound to the column was then eluted with a

linear gradient from 10 mM to 1 M NaCl in 20 mM MES buffer, pH 6 and fractions were collected. The fractions were assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that serine protease inhibitor proteins were not retained on the cation exchange column using the above conditions, and most of the serine protease inhibitor proteins were found in the flow-through fractions.

The cation exchange fractions containing the most serine protease inhibitor proteins were combined and concentrated to about 400 µl using an Ultrafree-20 15 ml centrifugal concentrator (available from Millipore Corp, Bedford, MA) in preparation for size exclusion chromatography. The sample was applied to a Bio-Select SEC 125-5 size exclusion chromatography column (available from Bio-Rad), previously equilibrated in TBS, pH 7.2. The column was eluted with TBS, pH 7.2 at a flow rate of about 0.5 ml/min, and fractions of about 250 µl were collected. Fractions were assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that serine protease inhibitor proteins were eluted in about 7 ml of buffer, corresponding to a molecular weight of about 30 kD to 66 kD based on the elution volumes of gel filtration molecular weight standard proteins (available from Sigma, St. Louis, MO).

The size exclusion chromatography fractions that contained the most serine protease inhibitor proteins were combined and brought to about 40% saturation with ammonium sulfate in preparation for hydrophobic interaction chromatography. The sample was applied to a 1 ml HighTrap™ Phenyl Sepharose® HP hydrophobic interaction chromatography column (available from Pharmacia) equilibrated with TBS, 40% saturated with ammonium sulfate. The column was washed with TBS, 40% saturated with ammonium sulfate until all unbound protein was removed. Bound protein was eluted from the column with a linear gradient from TBS, 40% saturated with ammonium sulfate to TBS with no ammonium sulfate. Fractions were assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that serine protease inhibitor proteins were eluted when the buffer was about 30% saturated with ammonium sulfate.

The hydrophobic interaction chromatography fractions that contained the most serine protease inhibitor proteins were combined and assayed for protein concentration using Micro BCA Protein Assay Reagent (available from Pierce, Rockford, IL) with bovine serum albumin as a standard. About 10 μg of serine protease inhibitor proteins were concentrated to about 20 μl using a Microcon 3 centrifugal concentrator (available from Amicon, Beverly, MA), resolved on a reducing 14% SDS-PAGE gel (available from Novex, San Diego, CA) and then blotted onto a polyvinylidene difluoride (PVDF) membrane (available from Applied Biosystems, Foster City, CA) for about 60 min in 10 mM CAPS buffer (3-[cyclohexylamino]-1-propanesulfonic acid; available from Sigma, St. Louis, MO), pH 11, with 0.5 mM dithiothreitol (DTT). The membrane was stained for 1 minute in 0.1% Coomassie Blue R-250 dissolved in 40% methanol and 1% acetic acid. The membrane was destained in 50% methanol for about 10 minutes, rinsed with water and air dried. A stained protein band was identified having an apparent molecular weight identical to the proteins identified by the immunoblot method described above, at about 36 kD. A portion of the membrane containing the band was excised, and protein contained in the membrane segment was subjected to N-terminal amino sequencing using a 473A Protein Sequencer (available from Applied Biosystems) and using standard techniques. The results indicated that the N-terminal amino acid sequence of the 36 kD protein was Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met (using standard 3 letter amino acid code), referred to herein as SEQ ID NO:88.

Example 13

This example describes the purification of serine protease inhibitor proteins from cat blood fed adult flea midguts.

About 45,000 cat blood-fed wandering larvae were homogenized by freeze-fracture and sonicated in Tris buffer comprising 50 mM Tris, pH 8 and 100 mM $CaCl_2$. The sonicates were clarified by centrifugation at about 14,000 x g for 20 min to produce an extract. Soluble protein in the extract was removed by aspiration and diluted to a volume of about 45 ml in Tris buffer. Sodium chloride was then added to the extract to bring the final concentration of NaCl to about 400 mM. The extract was then applied in two aliquots to a column containing about 1 ml of *p*-aminobenzamidine cross-linked to

Sepharose® beads, previously equilibrated in 50 mM Tris, pH 8, 400 mM NaCl. After an overnight incubation, the columns were drained and the flow-through fractions were retained. The flow-through fractions, which contained most of the midgut proteins except serine proteases, were combined and diafiltered into about 16 ml of 25 mM Tris, pH 8, containing 10 mM NaCl in preparation for anion exchange chromatography. Two aliquots of about 8 ml were then applied to an Uno Q6 column and fractions assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that the serine protease inhibitor proteins were eluted at about 160 mM NaCl.

The anion exchange column fractions that contained the most serine protease inhibitor proteins were pooled and diafiltered into a total of about 3 ml of 20 mM MES buffer, pH 6, containing 10 mM NaCl in preparation for cation exchange chromatography. The sample was then applied to an Uno S1 column and fractions assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that serine protease inhibitor proteins were not retained on the cation exchange column using the above conditions, and most of the serine protease inhibitor proteins were found in the flow-through fractions.

The cation exchange fractions that contained the most serine protease inhibitor proteins were combined and diafiltered into about 3 ml of 25 mM Tris, pH 8, containing 10 mM NaCl in preparation for anion exchange chromatography. The sample was applied to a Bio-Scale Q2 column (available from Bio-Rad), previously equilibrated in 25 mM Tris, pH 8, containing 10 mM NaCl. The column was washed with 25 mM Tris, pH 8, 10 mM NaCl until all unbound protein was removed. Protein bound to the column was then eluted with a linear gradient from 10 mM to 1 M NaCl in 25 mM Tris, pH 8. Fractions were assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5. The results indicated that serine protease inhibitor proteins were eluted at about 140 mM NaCl.

About 500 µl of the anion exchange column fraction that contained the most serine protease inhibitor protein was concentrated to about 25 µl using a Microcon 3

centrifugal concentrator (available from Amicon, Beverly, MA), and then separated by SDS-PAGE, electroblotted onto a PVDF membrane, and two stained protein bands, at about 35 kD and 36 kD, were N-terminally sequenced as described in Example 12. The results indicated that the N-terminal amino acid sequence of the 35 kD protein was Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met (using standard 3 letter amino acid code; referred to herein as SEQ ID NO:89) and the N-term sequence of the 36 kD protein was Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro (using standard 3 letter amino acid code; referred to herein as SEQ ID NO:90).

Example 14

This example describes the identification of serine protease inhibitor proteins in different flea tissues.

Tissue samples were isolated from unfed or bovine blood-fed 1st instar *Ctenocephalides felis* flea larvae; bovine blood-fed 3rd instar *C. felis* flea larvae, bovine blood-fed wandering *C. felis* flea larvae, unfed or cat blood-fed adult *C. felis* flea midgut tissue, cat blood-fed adult *C. felis* flea tissues that had their midguts and heads removed (adult partial fleas), and whole unfed or cat blood-fed adult *C. felis* fleas. The 1st instar, 3rd instar, wandering and adult midgut tissues were then homogenized by freeze-fracture and sonicated in Tris buffered saline (TBS). The adult partial fleas and adult whole fleas were then homogenized by freeze-fracture and ground with a microtube mortar and pestle. The extracts were centrifuged at about 14,000 x g for 20 min and the soluble material recovered. The soluble material was then diluted to a final concentration of about 1 tissue equivalent per 2 µl. Each soluble extract sample was then assayed for the presence of serine protease inhibitor proteins by immunoblot analysis using the anti-SPI2 polyclonal antiserum described in Example 5.

The results shown in Figure 1 indicated that all tissue extracts except the unfed 1st instar tissues contained proteins of about 25 kD to 97 kD that were cross reactive with the rabbit anti-SPI2 polyclonal antiserum, and were therefore comprised at least partially of serine protease inhibitor proteins.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Wisnewski, Nancy
Brandt, Kevin S.
Silver, Gary M.
Maddux, Joely D.

(ii) TITLE OF INVENTION: Novel Serine Protease Inhibitor Nucleic Acid Molecules, Proteins and Uses Thereof

(iii) NUMBER OF SEQUENCES: 98

(iv) CORRESPONDENCE ADDRESS:
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: Windows 95
(D) SOFTWARE: WordPerfect for Windows, Version 7.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Rothenberger, Scott D.
(B) REGISTRATION NUMBER: 41,277
(C) REFERENCE/DOCKET NUMBER: HKV-011PC

(viii) TELECOMMUNICATION INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1584 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(ix)  FEATURE:
      (A)  NAME/KEY:  CDS
      (B)  LOCATION:  136..1326

(xi)  SEQUENCE DESCRIPTION:  SEQ ID NO:1

GCCTGGAAGG TGATAAGTAA ACGGGCACGG TAGTGTTTTG TTTTAGAAAA TAATTTTAAT     60
TCGTACGACG TACGTTTTTG TGATTTTAAT TTTTTAGTGT TTTTGTAGCT CTGAAAGAGC    120

CGAAATTTTA GCAAA ATG ATT AAC GCA CGA CTT GTG TTT CTT TTT GTA TCA     171
                 Met Ile Asn Ala Arg Leu Val Phe Leu Phe Val Ser
                  1               5                  10

GTG TTA TTA CCA ATT TCA ACA ATG GCC GAT CCC CAG GAA TTG TCT ACA      219
Val Leu Leu Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr
        15                  20                  25

AGT ATT AAC CAG TTT GCT GGA AGC CTG TAC AAT ACA GTT GCT TCT GGC      267
Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly
    30                  35                  40

AAC AAA GAC AAT CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT CTA      315
Asn Lys Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu
 45                  50                  55                  60

TCC CTG GTG TCA ATG GGA GCT GGT GGC AAT ACT GCC ACA CAA ATA GCT      363
Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala
                 65                  70                  75

GCT GGT TTG CGT CAG CCT CAA TCA AAA GAA AAA ATT CAA GAT GAC TAC      411
Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr
            80                  85                  90

CAC GCA TTG ATG AAC ACT CTT AAT ACA CAA AAA GGT GTA ACT CTG GAA      459
His Ala Leu Met Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu
        95                 100                 105

ATT GCC AAT AAA GTT TAT GTT ATG GAA GGC TAT ACA TTA AAA CCC ACC      507
Ile Ala Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr
    110                 115                 120

TTC AAA GAA GTT GCC ACC AAC AAA TTC TTA GCT GGA GCA GAA AAC TTG      555
Phe Lys Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu
125                 130                 135                 140

AAC TTT GCC CAA AAT GCT GAA AGC GCT AAA GTT ATC AAC ACT TGG GTT      603
Asn Phe Ala Gln Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val
                145                 150                 155

GAA GAA AAA ACT CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT GAT      651
Glu Glu Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp
            160                 165                 170

CTA GAC CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC TTC AAG      699
Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys
        175                 180                 185

GGT CTT TGG GAG AAA CAA TTC AAA AAG GAA AAT ACC CAA GAC AAA CCT      747
Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro
    190                 195                 200
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TTC TAT GTT ACT GAA ACA GAG ACA AAG AAT GTA CGA ATG ATG CAC ATT      795
Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile
205                 210                 215                 220

AAG GAT AAA TTC CGT TAT GGA GAA TTT GAA GAA TTA GAT GCC AAG GCT      843
Lys Asp Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala
                225                 230                 235

GTA GAA TTG CCC TAC AGG AAC TCA GAT TTG GCC ATG TTA ATC ATT TTG      891
Val Glu Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu
            240                 245                 250

CCA AAC AGC AAA ACT GGT CTC CCC GCT CTT GAA GAA AAA TTA CAA AAT      939
Pro Asn Ser Lys Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn
        255                 260                 265

GTT GAT TTG CAA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT      987
Val Asp Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile
    270                 275                 280

TTG GAT CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT     1035
Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
285                 290                 295                 300

CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT     1083
Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala
                305                 310                 315

GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT     1131
Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
            320                 325                 330

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT GCT GAA     1179
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu
        335                 340                 345

GCT GCA GCT GCC ACA GCT ACC TTT ATG GTT ACC TAT GAA CTG GAG GTT     1227
Ala Ala Ala Ala Thr Ala Thr Phe Met Val Thr Tyr Glu Leu Glu Val
    350                 355                 360

TCC CTG GAT CTT CCC ACT GTT TTT AAA GTC GAT CAT CCA TTC AAT ATT     1275
Ser Leu Asp Leu Pro Thr Val Phe Lys Val Asp His Pro Phe Asn Ile
365                 370                 375                 380

GTT TTG AAG ACA GGT GAT ACT GTT ATT TTT AAT GGG CGA GTT CAA ACT     1323
Val Leu Lys Thr Gly Asp Thr Val Ile Phe Asn Gly Arg Val Gln Thr
                385                 390                 395

TTA TAA AATGGATAGT GTAAAAAGAA TACAAGATCT ATCTGAATCT CTGGATTAAT      1379
Leu

GAAGTAATTT TTCTACAATA TTTTTTAATA GTTATTAGGT CTAAAATAAG TTCATTTTTT  1439
AGTATGTGGT ATAAATCGTG TAGACGAAAA ATGTTTTGTT TTAGTTTTCA CTTTTTATGA  1499
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AAAAAAAAAA AAAAAAAAAA AAAAA                                         1584
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 397 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Ile Asn Ala Arg Leu Val Phe Leu Phe Val Ser Val Leu Leu Pro
 1               5                  10                  15

Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln
            20                  25                  30

Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn
        35                  40                  45

Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser
    50                  55                  60

Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg
65                  70                  75                  80

Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met
                85                  90                  95

Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys
            100                 105                 110

Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val
        115                 120                 125

Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln
    130                 135                 140

Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr
145                 150                 155                 160

His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp
                165                 170                 175

Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu
            180                 185                 190

Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr
        195                 200                 205

Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp Lys Phe
    210                 215                 220

Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro
225                 230                 235                 240

Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys
                245                 250                 255

Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln
            260                 265                 270

Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro
        275                 280                 285

Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
    290                 295                 300
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Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly
305                 310                 315                 320

Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln
                325                 330                 335

Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala
            340                 345                 350

Thr Ala Thr Phe Met Val Thr Tyr Glu Leu Glu Val Ser Leu Asp Leu
        355                 360                 365

Pro Thr Val Phe Lys Val Asp His Pro Phe Asn Ile Val Leu Lys Thr
    370                 375                 380

Gly Asp Thr Val Ile Phe Asn Gly Arg Val Gln Thr Leu
385                 390                 395
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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1584 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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GTCTACACGA TTTATACCAC ATACTAAAAA ATGAACTTAT TTTAGACCTA ATAACTATTA    180
AAAAATATTG TAGAAAAATT ACTTCATTAA TCCAGAGATT CAGATAGATC TTGTATTCTT    240
TTTACACTAT CCATTTTATA AAGTTTGAAC TCGCCCATTA AAAATAACAG TATCACCTGT    300
CTTCAAAACA ATATTGAATG GATGATCGAC TTTAAAAACA GTGGGAAGAT CCAGGGAAAC    360
CTCCAGTTCA TAGGTAACCA TAAAGGTAGC TGTGGCAGCT GCAGCTTCAG CACCTTCTTC    420
ATTTACTTCA ATGAAAGCTT TTTGAATTAC TTTAGAAATA TATAACATCT CATCAGATCC    480
TTCAAGCAAT CCTTTGAAAT CAGCTTTTCC AGGAACAAAC ATATCAGACA TACCCAACTT    540
TTTCAGAGGA TCATTCAAAT TAATTTCAGA TTCAATCTTG AATTTAGGCA GATCCAAAAT    600
AACTTCAACA GAGTACATGC GTTGAGTCAA GTTTTGCAAA TCAACATTTT GTAATTTTTC    660
TTCAAGAGCG GGGAGACCAG TTTTGCTGTT TGGCAAAATG ATTAACATGG CCAAATCTGA    720
GTTCCTGTAG GGCAATTCTA CAGCCTTGGC ATCTAATTCT TCAAATTCTC CATAACGGAA    780
TTTATCCTTA ATGTGCATCA TTCGTACATT CTTTGTCTCT GTTTCAGTAA CATAGAAAGG    840
TTTGTCTTGG GTATTTTCCT TTTTGAATTG TTTCTCCCAA AGACCCTTGA AGTACAATGC    900
ATTGACAAGA ACCATTCTTG AATCCTGGTC TAGATCACCG GCTTTGATCA AATCATGAAT    960
TTTGTCATGA GTTTTTTCTT CAACCCAAGT GTTGATAACT TTAGCGCTTT CAGCATTTTG   1020
GGCAAAGTTC AAGTTTTCTG CTCCAGCTAA GAATTTGTTG GTGGCAACTT CTTTGAAGGT   1080
GGGTTTTAAT GTATAGCCTT CCATAACATA AACTTTATTG GCAATTTCCA GAGTTACACC   1140
TTTTTGTGTA TTAAGAGTGT TCATCAATGC GTGGTAGTCA TCTTGAATTT TTTCTTTTGA   1200
TTGAGGCTGA CGCAAACCAG CAGCTATTTG TGTGGCAGTA TTGCCACCAG CTCCCATTGA   1260
CACCAGGGAT AGAACAGTTT GTACAGACAA TGGGGACATG ATGAGATTGT CTTTGTTGCC   1320
AGAAGCAACT GTATTGTACA GGCTTCCAGC AAACTGGTTA ATACTTGTAG ACAATTCCTG   1380
GGGATCGGCC ATTGTTGAAA TTGGTAATAA CACTGATACA AAAAGAAACA CAAGTCGTGC   1440
GTTAATCATT TTGCTAAAAT TTCGGCTCTT TCAGAGCTAC AAAAACACTA AAAAATTAAA   1500
ATCACAAAAA CGTACGTCGT ACGAATTAAA ATTATTTTCT AAAACAAAAC ACTACCGTGC   1560
CCGTTTACTT ATCACCTTCC AGGC                                          1584
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1191 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
ATGATTAACG CACGACTTGT GTTTCTTTTT GTATCAGTGT TATTACCAAT TTCAACAATG    60
GCCGATCCCC AGGAATTGTC TACAAGTATT AACCAGTTTG CTGGAAGCCT GTACAATACA   120
GTTGCTTCTG GCAACAAAGA CAATCTCATC ATGTCCCCAT TGTCTGTACA AACTGTTCTA   180
TCCCTGGTGT CAATGGGAGC TGGTGGCAAT ACTGCCACAC AAATAGCTGC TGGTTTGCGT   240
CAGCCTCAAT CAAAAGAAAA AATTCAAGAT GACTACCACG CATTGATGAA CACTCTTAAT   300
ACACAAAAAG GTGTAACTCT GGAAATTGCC AATAAAGTTT ATGTTATGGA AGGCTATACA   360
TTAAAACCCA CCTTCAAAGA AGTTGCCACC AACAAATTCT TAGCTGGAGC AGAAAACTTG   420
AACTTTGCCC AAAATGCTGA AAGCGCTAAA GTTATCAACA CTTGGGTTGA AGAAAAAACT   480
CATGACAAAA TTCATGATTT GATCAAAGCC GGTGATCTAG ACCAGGATTC AAGAATGGTT   540
CTTGTCAATG CATTGTACTT CAAGGGTCTT TGGGAGAAAC AATTCAAAAA GGAAAATACC   600
CAAGACAAAC CTTTCTATGT TACTGAAACA GAGACAAAGA ATGTACGAAT GATGCACATT   660
AAGGATAAAT TCCGTTATGG AGAATTTGAA GAATTAGATG CCAAGGCTGT AGAATTGCCC   720
TACAGGAACT CAGATTTGGC CATGTTAATC ATTTTGCCAA ACAGCAAAAC TGGTCTCCCC   780
GCTCTTGAAG AAAAATTACA AAATGTTGAT TTGCAAAACT TGACTCAACG CATGTACTCT   840
GTTGAAGTTA TTTTGGATCT GCCTAAATTC AAGATTGAAT CTGAAATTAA TTTGAATGAT   900
CCTCTGAAAA AGTTGGGTAT GTCTGATATG TTTGTTCCTG GAAAAGCTGA TTTCAAAGGA   960
TTGCTTGAAG GATCTGATGA GATGTTATAT ATTTCTAAAG TAATTCAAAA AGCTTTCATT  1020
GAAGTAAATG AAGAAGGTGC TGAAGCTGCA GCTGCCACAG CTACCTTTAT GGTTACCTAT  1080
GAACTGGAGG TTTCCCTGGA TCTTCCCACT GTTTTTAAAG TCGATCATCC ATTCAATATT  1140
GTTTTGAAGA CAGGTGATAC TGTTATTTTT AATGGGCGAG TTCAAACTTT A           1191
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1191 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
TAAAGTTTGA ACTCGCCCAT TAAAAATAAC AGTATCACCT GTCTTCAAAA CAATATTGAA    60
TGGATGATCG ACTTTAAAAA CAGTGGGAAG ATCCAGGGAA ACCTCCAGTT CATAGGTAAC   120
CATAAAGGTA GCTGTGGCAG CTGCAGCTTC AGCACCTTCT TCATTTACTT CAATGAAAGC   180
TTTTTGAATT ACTTTAGAAA TATATAACAT CTCATCAGAT CCTTCAAGCA ATCCTTTGAA   240
ATCAGCTTTT CCAGGAACAA ACATATCAGA CATACCCAAC TTTTTCAGAG GATCATTCAA   300
ATTAATTTCA GATTCAATCT TGAATTTAGG CAGATCCAAA ATAACTTCAA CAGAGTACAT   360
GCGTTGAGTC AAGTTTTGCA AATCAACATT TTGTAATTTT TCTTCAAGAG CGGGGAGACC   420
AGTTTTGCTG TTTGGCAAAA TGATTAACAT GGCCAAATCT GAGTTCCTGT AGGGCAATTC   480
TACAGCCTTG GCATCTAATT CTTCAAATTC TCCATAACGG AATTTATCCT TAATGTGCAT   540
CATTCGTACA TTCTTTGTCT CTGTTTCAGT AACATAGAAA GGTTTGTCTT GGGTATTTTC   600
CTTTTTGAAT TGTTTCTCCC AAAGACCCTT GAAGTACAAT GCATTGACAA GAACCATTCT   660
TGAATCCTGG TCTAGATCAC CGGCTTTGAT CAAATCATGA ATTTTGTCAT GAGTTTTTTC   720
TTCAACCCAA GTGTTGATAA CTTTAGCGCT TTCAGCATTT TGGGCAAAGT TCAAGTTTTC   780
TGCTCCAGCT AAGAATTTGT TGGTGGCAAC TTCTTTGAAG GTGGGTTTTA ATGTATAGCC   840
TTCCATAACA TAAACTTTAT TGGCAATTTC CAGAGTTACA CCTTTTTGTG TATTAAGAGT   900
GTTCATCAAT GCGTGGTAGT CATCTTGAAT TTTTTCTTTT GATTGAGGCT GACGCAAACC   960
AGCAGCTATT TGTGTGGCAG TATTGCCACC AGCTCCCATT GACACCAGGG ATAGAACAGT  1020
```

```
TTGTACAGAC AATGGGGACA TGATGAGATT GTCTTTGTTG CCAGAAGCAA CTGTATTGTA  1080
CAGGCTTCCA GCAAACTGGT TAATACTTGT AGACAATTCC TGGGGATCGG CCATTGTTGA  1140
AATTGGTAAT AACACTGATA CAAAAAGAAA CACAAGTCGT GCGTTAATCA T           1191
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 376 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu
 1               5                  10                  15

Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
            20                  25                  30

Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly
        35                  40                  45

Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys
    50                  55                  60

Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr
65                  70                  75                  80

Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu
                85                  90                  95

Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe
            100                 105                 110

Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala
        115                 120                 125

Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His
    130                 135                 140

Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu
145                 150                 155                 160

Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys
                165                 170                 175

Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys
            180                 185                 190

Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe
        195                 200                 205

Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp
    210                 215                 220

Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala
225                 230                 235                 240

Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg
                245                 250                 255
```

```
Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu
            260                 265                 270

Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp
        275                 280                 285

Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser
    290                 295                 300

Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu
305                 310                 315                 320

Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Thr Phe Met
                325                 330                 335

Val Thr Tyr Glu Leu Glu Val Ser Leu Asp Leu Pro Thr Val Phe Lys
            340                 345                 350

Val Asp His Pro Phe Asn Ile Val Leu Lys Thr Gly Asp Thr Val Ile
        355                 360                 365

Phe Asn Gly Arg Val Gln Thr Leu
    370                 375
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1358 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
- (A) NAME/KEY: CDS
- (B) LOCATION: 2..1198

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
C GCG ATA GTT CAA CAC GCA CGA CTT GTG TTT CTT TTT GTA TCA GTG        46
  Ala Ile Val Gln His Ala Arg Leu Val Phe Leu Phe Val Ser Val
    1               5                  10                  15

TTA ATA CCA ATT TCA ACA ATG GCG GAT CCC CAG GAA TTG TCT ACA AGT      94
Leu Ile Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr Ser
                20                  25                  30

ATT AAC CAG TTT GCT GGA AGC CTG TAC AAT ACG GTT GCT TCT GGC AAC     142
Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn
            35                  40                  45

AAA GAC AAT CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT CTA TCC     190
Lys Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser
        50                  55                  60

CTG GTG TCA ATG GGA GCT GGT GGT AAT ACT GCC ACA CAA ATA GCT GCT     238
Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala
    65                  70                  75
```

GGT TTA CGT CAG CCT CAA TCA AAA GAA AAA ATT CAA GAT GAC TAC CAT 286
Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His
80 85 90 95

GCA TTG ATG AAC ACT CTT AAT ACA CAA AAA GGT GTA ACT CTG GAA ATT 334
Ala Leu Met Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile
100 105 110

GCC AAC AAA GTT TAC GTT ATG GAA GGC TAT ACA TTG AAA CCC ACC TTC 382
Ala Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe
115 120 125

AAA GAA GTT GCC ACC AAC AAA TTC TTA GCT GGA GCA GAA AAC TTG AAC 430
Lys Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn
130 135 140

TTT GCC CAA AAT GCT GAA AGC GCT AAA GTT ATC AAC ACT TGG GTT GAA 478
Phe Ala Gln Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu
145 150 155

GAA AAA ACT CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT GAT CTA 526
Glu Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu
160 165 170 175

GAC CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC TTC AAG GGT 574
Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys Gly
180 185 190

CTT TGG GAG AAA CAA TTC AAG AAG GAA AAC ACT CAA GAC AAA CCT TTC 622
Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe
195 200 205

TAT GTT ACT GAA ACA GAG ACA AAG AAT GTA CGA ATG ATG CAC ATT AAG 670
Tyr Val Thr Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys
210 215 220

GAT AAA TTC CGT TAT GGA GAA TTT GAA GAA TTA GAT GCC AAG GCT GTA 718
Asp Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala Val
225 230 235

GAA TTG CCC TAC AGG AAC TCA GAT TTG GCC ATG TTA ATC ATT TTG CCA 766
Glu Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro
240 245 250 255

AAC AGC AAA ACT GGT CTC CCC GCT CTT GAA GAA AAA TTA CAA AAT GTT 814
Asn Ser Lys Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val
260 265 270

GAC TTG CAA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG 862
Asp Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu
275 280 285

GAT CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT 910
Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro
290 295 300

CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT 958
Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp
305 310 315

```
TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT AAA     1006
Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys
320                 325                 330                 335

GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT GCT GAA GCT     1054
Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu Ala
                340                 345                 350

GCA GCT GCC ACA GGC ATT GTC ATG CTT GGT TGC TGT ATG CCA ATG ATG     1102
Ala Ala Ala Thr Gly Ile Val Met Leu Gly Cys Cys Met Pro Met Met
            355                 360                 365

GAT CTT TCT CCA GTA GTT TTT AAT ATT GAT CAC CCA TTT TAT TAC TCA     1150
Asp Leu Ser Pro Val Val Phe Asn Ile Asp His Pro Phe Tyr Tyr Ser
        370                 375                 380

TTG ATG ACT TGG GAT ACT GTT TTG TTC AGT GGA TGT GTT AAA TCC CTT     1198
Leu Met Thr Trp Asp Thr Val Leu Phe Ser Gly Cys Val Lys Ser Leu
    385                 390                 395

TAA ATTTCTTCTT AGAATGAAGG TATTTCAGTG TCTAATGGCA TTGATAGACC          1251
CAAAAATTTC AATTCTGACC ATGCTTTCTA CCTCATGATA ACGGCAGGGA AAACGATTTC   1311
AATTAGAGGT CGTTTCTATA ACTCCTAGTA TATGTTATAT GACTAGT                 1358
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 399 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Ala Ile Val Gln His Ala Arg Leu Val Phe Leu Phe Val Ser Val Leu
 1               5                  10                  15

Ile Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile
            20                  25                  30

Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys
        35                  40                  45

Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu
    50                  55                  60

Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly
65                  70                  75                  80

Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala
                85                  90                  95

Leu Met Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala
            100                 105                 110

Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys
        115                 120                 125

Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe
    130                 135                 140
```

Ala Gln Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu
145 150 155 160

Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp
165 170 175

Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu
180 185 190

Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr
195 200 205

Val Thr Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp
210 215 220

Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala Val Glu
225 230 235 240

Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn
245 250 255

Ser Lys Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp
260 265 270

Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
275 280 285

Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu
290 295 300

Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
305 310 315 320

Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val
325 330 335

Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu Ala Ala
340 345 350

Ala Ala Thr Gly Ile Val Met Leu Gly Cys Cys Met Pro Met Met Asp
355 360 365

Leu Ser Pro Val Val Phe Asn Ile Asp His Pro Phe Tyr Tyr Ser Leu
370 375 380

Met Thr Trp Asp Thr Val Leu Phe Ser Gly Cys Val Lys Ser Leu
385 390 395

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1358 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACTAGTCATA TAACATATAC TAGGAGTTAT AGAAACGACC TCTAATTGAA ATCGTTTTCC 60
CTGCCGTTAT CATGAGGTAG AAAGCATGGT CAGAATTGAA ATTTTTGGGT CTATCAATGC 120

```
CATTAGACAC TGAAATACCT TCATTCTAAG AAGAAATTTA AAGGGATTTA ACACATCCAC   180
TGAACAAAAC AGTATCCCAA GTCATCAATG AGTAATAAAA TGGGTGATCA ATATTAAAAA   240
CTACTGGAGA AAGATCCATC ATTGGCATAC AGCAACCAAG CATGACAATG CCTGTGGCAG   300
CTGCAGCTTC AGCACCTTCT TCATTTACTT CAATGAAAGC TTTTTGAATT ACTTTAGAAA   360
TATATAACAT CTCATCAGAT CCTTCAAGCA ATCCTTTGAA ATCAGCTTTT CCAGGAACAA   420
ACATATCAGA CATACCCAAC TTTTTCAGAG GATCATTCAA ATTAATTTCA GATTCAATCT   480
TGAATTTAGG CAGATCCAAA ATAACTTCAA CAGAGTACAT GCGTTGAGTC AAGTTTTGCA   540
AGTCAACATT TTGTAATTTT TCTTCAAGAG CGGGGAGACC AGTTTTGCTG TTTGGCAAAA   600
TGATTAACAT GGCCAAATCT GAGTTCCTGT AGGGCAATTC TACAGCCTTG GCATCTAATT   660
CTTCAAATTC TCCATAACGG AATTTATCCT TAATGTGCAT CATTCGTACA TTCTTTGTCT   720
CTGTTTCAGT AACATAGAAA GGTTTGTCTT GAGTGTTTTC CTTCTTGAAT TGTTTCTCCC   780
AAAGACCCTT GAAGTACAAT GCATTGACAA GAACCATTCT TGAATCCTGG TCTAGATCAC   840
CGGCTTTGAT CAAATCATGA ATTTTGTCAT GAGTTTTTTC TTCAACCCAA GTGTTGATAA   900
CTTTAGCGCT TTCAGCATTT TGGGCAAAGT TCAAGTTTTC TGCTCCAGCT AAGAATTTGT   960
TGGTGGCAAC TTCTTTGAAG GTGGGTTTCA ATGTATAGCC TTCCATAACG TAAACTTTGT  1020
TGGCAATTTC CAGAGTTACA CCTTTTTGTG TATTAAGAGT GTTCATCAAT GCATGGTAGT  1080
CATCTTGAAT TTTTTCTTTT GATTGAGGCT GACGTAAACC AGCAGCTATT TGTGTGGCAG  1140
TATTACCACC AGCTCCCATT GACACCAGGG ATAGAACAGT TTGTACAGAC AATGGGGACA  1200
TGATGAGATT GTCTTTGTTG CCAGAAGCAA CCGTATTGTA CAGGCTTCCA GCAAACTGGT  1260
TAATACTTGT AGACAATTCC TGGGGATCCG CCATTGTTGA AATTGGTATT AACACTGATA  1320
CAAAAAGAAA CACAAGTCGT GCGTGTTGAA CTATCGCG                          1358
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1197 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
GCGATAGTTC AACACGCACG ACTTGTGTTT CTTTTTGTAT CAGTGTTAAT ACCAATTTCA    60
ACAATGGCGG ATCCCCAGGA ATTGTCTACA AGTATTAACC AGTTTGCTGG AAGCCTGTAC   120
AATACGGTTG CTTCTGGCAA CAAAGACAAT CTCATCATGT CCCCATTGTC TGTACAAACT   180
GTTCTATCCC TGGTGTCAAT GGGAGCTGGT GGTAATACTG CCACACAAAT AGCTGCTGGT   240
TTACGTCAGC CTCAATCAAA AGAAAAAATT CAAGATGACT ACCATGCATT GATGAACACT   300
CTTAATACAC AAAAAGGTGT AACTCTGGAA ATTGCCAACA AAGTTTACGT TATGGAAGGC   360
TATACATTGA AACCCACCTT CAAAGAAGTT GCCACCAACA AATTCTTAGC TGGAGCAGAA   420
AACTTGAACT TTGCCCAAAA TGCTGAAAGC GCTAAAGTTA TCAACACTTG GGTTGAAGAA   480
AAAACTCATG ACAAAATTCA TGATTTGATC AAAGCCGGTG ATCTAGACCA GGATTCAAGA   540
ATGGTTCTTG TCAATGCATT GTACTTCAAG GGTCTTTGGG AGAAACAATT CAAGAAGGAA   600
AACACTCAAG ACAAACCTTT CTATGTTACT GAAACAGAGA CAAAGAATGT ACGAATGATG   660
CACATTAAGG ATAAATTCCG TTATGGAGAA TTTGAAGAAT TAGATGCCAA GGCTGTAGAA   720
TTGCCCTACA GGAACTCAGA TTTGGCCATG TTAATCATTT TGCCAAACAG CAAAACTGGT   780
CTCCCCGCTC TTGAAGAAAA ATTACAAAAT GTTGACTTGC AAAACTTGAC TCAACGCATG   840
TACTCTGTTG AAGTTATTTT GGATCTGCCT AAATTCAAGA TTGAATCTGA AATTAATTTG   900
AATGATCCTC TGAAAAAGTT GGGTATGTCT GATATGTTTG TTCCTGGAAA AGCTGATTTC   960
AAAGGATTGC TTGAAGGATC TGATGAGATG TTATATATTT CTAAAGTAAT TCAAAAAGCT  1020
TTCATTGAAG TAAATGAAGA AGGTGCTGAA GCTGCAGCTG CCACAGGCAT TGTCATGCTT  1080
GGTTGCTGTA TGCCAATGAT GGATCTTTCT CCAGTAGTTT TTAATATTGA TCACCCATTT  1140
TATTACTCAT TGATGACTTG GGATACTGTT TTGTTCAGTG GATGTGTTAA ATCCCTT     1197
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1197 nucleic acid
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
AAGGGATTTA ACACATCCAC TGAACAAAAC AGTATCCCAA GTCATCAATG AGTAATAAAA     60
TGGGTGATCA ATATTAAAAA CTACTGGAGA AAGATCCATC ATTGGCATAC AGCAACCAAG    120
CATGACAATG CCTGTGGCAG CTGCAGCTTC AGCACCTTCT TCATTTACTT CAATGAAAGC    180
TTTTTGAATT ACTTTAGAAA TATATAACAT CTCATCAGAT CCTTCAAGCA ATCCTTTGAA    240
ATCAGCTTTT CCAGGAACAA ACATATCAGA CATACCCAAC TTTTTCAGAG GATCATTCAA    300
ATTAATTTCA GATTCAATCT TGAATTTAGG CAGATCCAAA ATAACTTCAA CAGAGTACAT    360
GCGTTGAGTC AAGTTTTGCA AGTCAACATT TTGTAATTTT TCTTCAAGAG CGGGGAGACC    420
AGTTTTGCTG TTTGGCAAAA TGATTAACAT GGCCAAATCT GAGTTCCTGT AGGGCAATTC    480
TACAGCCTTG GCATCTAATT CTTCAAATTC TCCATAACGG AATTTATCCT TAATGTGCAT    540
CATTCGTACA TTCTTTGTCT CTGTTTCAGT AACATAGAAA GGTTTGTCTT GAGTGTTTTC    600
CTTCTTGAAT TGTTTCTCCC AAAGACCCTT GAAGTACAAT GCATTGACAA GAACCATTCT    660
TGAATCCTGG TCTAGATCAC CGGCTTTGAT CAAATCATGA ATTTTGTCAT GAGTTTTTTC    720
TTCAACCCAA GTGTTGATAA CTTTAGCGCT TTCAGCATTT TGGGCAAAGT TCAAGTTTTC    780
TGCTCCAGCT AAGAATTTGT TGGTGGCAAC TTCTTTGAAG GTGGGTTTCA ATGTATAGCC    840
TTCCATAACG TAAACTTTGT TGGCAATTTC CAGAGTTACA CCTTTTTGTG TATTAAGAGT    900
GTTCATCAAT GCATGGTAGT CATCTTGAAT TTTTTCTTTT GATTGAGGCT GACGTAAACC    960
AGCAGCTATT TGTGTGGCAG TATTACCACC AGCTCCCATT GACACCAGGG ATAGAACAGT   1020
TTGTACAGAC AATGGGGACA TGATGAGATT GTCTTTGTTG CCAGAAGCAA CCGTATTGTA   1080
CAGGCTTCCA GCAAACTGGT TAATACTTGT AGACAATTCC TGGGGATCCG CCATTGTTGA   1140
AATTGGTATT AACACTGATA CAAAAAGAAA CACAAGTCGT GCGTGTTGAA CTATCGC      1197
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 376 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu
 1               5                  10                  15

Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
            20                  25                  30

Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly
        35                  40                  45

Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys
    50                  55                  60

Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr
65                  70                  75                  80

Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu
                85                  90                  95

Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe
            100                 105                 110

Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala
        115                 120                 125

Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His
    130                 135                 140
```

```
Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu
145                 150                 155                 160

Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys
                165                 170                 175

Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys
            180                 185                 190

Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe
        195                 200                 205

Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp
    210                 215                 220

Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala
225                 230                 235                 240

Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg
                245                 250                 255

Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu
            260                 265                 270

Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp
        275                 280                 285

Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser
    290                 295                 300

Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu
305                 310                 315                 320

Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Ile Val Met
                325                 330                 335

Leu Gly Cys Cys Met Pro Met Met Asp Leu Ser Pro Val Val Phe Asn
            340                 345                 350

Ile Asp His Pro Phe Tyr Tyr Ser Leu Met Thr Trp Asp Thr Val Leu
        355                 360                 365

Phe Ser Gly Cys Val Lys Ser Leu
    370                 375
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1838 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 306..1565

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

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ATTGTGCAAA GTCAAATTAC GCATTTAGAA TATTAAAATC AGTATCTCCA AAAATACATA      60
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CAAATCAATT CAATAACTAT CATTCAAATG ACATCATGTT CAAAATAAAT TAAACACAAA   120
TATAAAAATG AAGCTAATTT TTGGAAACTG TGTGATTCCA AGGACGACAG AAATATAAAA   180
CAGATTCATG TGTGTTGTTC CGCGAAGCCA AATGTTTGAA TGTATATAGT GTGTTATTCA   240
AACATTCCTA GTATTTCTAT ATTATACAAT ATGACTCACA AACGATTCTA ATATCTAGAG   300

TTTTG ATG CCG CGT CCT CAG TTT GAC GCG ATA GTT CAA CAC GCA CGA CTT   350
      Met Pro Arg Pro Gln Phe Asp Ala Ile Val Gln His Ala Arg Leu
       1               5                  10                  15

GTG TTT CTT TTT GTA TCA GTG TTA ATA CCA ATT TCA ACA ATG GCG GAT     398
Val Phe Leu Phe Val Ser Val Leu Ile Pro Ile Ser Thr Met Ala Asp
                20                  25                  30

CCC CAG GAA TTG TCT ACA AGT ATT AAC CAG TTT GCT GGA AGC CTG TAC     446
Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr
            35                  40                  45

AAT ACG GTT GCT TCT GGC AAC AAA GAC AAT CTC ATC ATG TCC CCA TTG     494
Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro Leu
        50                  55                  60

TCT GTA CAA ACT GTT CTA TCC CTG GTG TCA ATG GGA GCT GGT GGT AAT     542
Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly Asn
    65                  70                  75

ACT GCC ACA CAA ATA GCT GCT GGT TTA CGT CAG CCT CAA TCA AAA GAA     590
Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu
 80                  85                  90                  95

AAA ATT CAA GAT GAC TAC CAT GCA TTG ATG AAC ACT CTT AAT ACA CAA     638
Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln
                100                 105                 110

AAA GGT GTA ACT CTG GAA ATT GCC AAC AAA GTT TAC GTT ATG GAA GGC     686
Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu Gly
            115                 120                 125

TAT ACA TTG AAA CCC ACC TTC AAA GAA GTT GCC ACC AAC AAA TTC TTA     734
Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe Leu
        130                 135                 140

GCT GGA GCA GAA AAC TTG AAC TTT GCC CAA AAT GCT GAA AGC GCT AAA     782
Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala Lys
    145                 150                 155

GTT ATC AAC ACT TGG GTT GAA GAA AAA ACT CAT GAC AAA ATT CAT GAT     830
Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His Asp
160                 165                 170                 175

TTG ATC AAA GCC GGT GAT CTA GAC CAG GAT TCA AGA ATG GTT CTT GTC     878
Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu Val
                180                 185                 190

AAT GCA TTG TAC TTC AAG GGT CTT TGG GAG AAA CAA TTC AAG AAG GAA     926
Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu
            195                 200                 205

AAC ACT CAA GAC AAA CCT TTC TAT GTT ACT GAA ACA GAG ACA AAG AAT     974
Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn
        210                 215                 220
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GTA CGA ATG ATG CAC ATT AAG GAT AAA TTC CGT TAT GGA GAA TTT GAA     1022
Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe Glu
    225                 230                 235

GAA TTA GAT GCC AAG GCT GTA GAA TTG CCC TAC AGG AAC TCA GAT TTG     1070
Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp Leu
240                 245                 250                 255

GCC ATG TTA ATC ATT TTG CCA AAC AGC AAA ACT GGT CTC CCC GCT CTT     1118
Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala Leu
                260                 265                 270

GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA CGC ATG     1166
Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg Met
            275                 280                 285

TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC AAG ATT GAA TCT     1214
Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser
        290                 295                 300

GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG     1262
Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met
    305                 310                 315

TTT GTT CCT GGA AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT     1310
Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp
320                 325                 330                 335

GAG ATG TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA     1358
Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
                340                 345                 350

AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GCG GTG CTT TTA GTA     1406
Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Val Leu Leu Val
            355                 360                 365

ACG GAA TCT TAT GTA CCT GAG GAA GTA TTC GAA GCT AAT CAT CCC TTT     1454
Thr Glu Ser Tyr Val Pro Glu Glu Val Phe Glu Ala Asn His Pro Phe
        370                 375                 380

TAT TTT GCA CTC TAT AAA TCT GCA CAA AAT CCA GTA GAA TCT GAA AAT     1502
Tyr Phe Ala Leu Tyr Lys Ser Ala Gln Asn Pro Val Glu Ser Glu Asn
    385                 390                 395

GAA AGC TCT GAA AAT GAA AAC CCT GAA AAT GTT GAA GTA CTA TTC TCT     1550
Glu Ser Ser Glu Asn Glu Asn Pro Glu Asn Val Glu Val Leu Phe Ser
400                 405                 410                 415

GGG AGA TTT ACC AAT TAG AAAAATATGT GTTACTAGCC TTGTGATTAT            1598
Gly Arg Phe Thr Asn
                420

AAGCAGGACA AATTTCAAAA ATACAAGATC TATCTGAATC TCTGGATTAA TGAAGTAATT   1658
TTTCTACAAT ATTTTTTAAT AGTTATTAGG TCTAAAATAA GTTCATTTTT TAGTATGTGG   1718
TATAAATCGT GTAGACGAAA AATGTTTTGT TTTAGTTTTC ACTTTTTATG AATGTAATCA   1778
CCTATATAAT GTTGTAGTTT ATGTAATAAA AATGTTAAAT GTGAAAAAAA AAAAAAAAAA   1838
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 420 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Met Pro Arg Pro Gln Phe Asp Ala Ile Val Gln His Ala Arg Leu Val
 1               5                  10                  15

Phe Leu Phe Val Ser Val Leu Ile Pro Ile Ser Thr Met Ala Asp Pro
            20                  25                  30

Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn
        35                  40                  45

Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro Leu Ser
    50                  55                  60

Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr
65                  70                  75                  80

Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys
                85                  90                  95

Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln Lys
            100                 105                 110

Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu Gly Tyr
        115                 120                 125

Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe Leu Ala
    130                 135                 140

Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala Lys Val
145                 150                 155                 160

Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His Asp Leu
                165                 170                 175

Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn
            180                 185                 190

Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn
        195                 200                 205

Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn Val
    210                 215                 220

Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe Glu Glu
225                 230                 235                 240

Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp Leu Ala
                245                 250                 255

Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala Leu Glu
            260                 265                 270
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Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg Met Tyr
        275                 280                 285

Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu
    290                 295                 300

Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe
305                 310                 315                 320

Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu
                325                 330                 335

Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn
            340                 345                 350

Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Val Leu Leu Val Thr
        355                 360                 365

Glu Ser Tyr Val Pro Glu Glu Val Phe Glu Ala Asn His Pro Phe Tyr
    370                 375                 380

Phe Ala Leu Tyr Lys Ser Ala Gln Asn Pro Val Glu Ser Glu Asn Glu
385                 390                 395                 400

Ser Ser Glu Asn Glu Asn Pro Glu Asn Val Glu Val Leu Phe Ser Gly
                405                 410                 415

Arg Phe Thr Asn
            420
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1838 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
TTTTTTTTTT TTTTTTTCAC ATTTAACATT TTTATTACAT AAACTACAAC ATTATATAGG     60
TGATTACATT CATAAAAAGT GAAAACTAAA ACAAAACATT TTTCGTCTAC ACGATTTATA    120
CCACATACTA AAAAATGAAC TTATTTTAGA CCTAATAACT ATTAAAAAAT ATTGTAGAAA    180
AATTACTTCA TTAATCCAGA GATTCAGATA GATCTTGTAT TTTTGAAATT TGTCCTGCTT    240
ATAATCACAA GGCTAGTAAC ACATATTTTT CTAATTGGTA AATCTCCCAG AGAATAGTAC    300
TTCAACATTT TCAGGGTTTT CATTTTCAGA GCTTTCATTT TCAGATTCTA CTGGATTTTG    360
TGCAGATTTA TAGAGTGCAA AATAAAAGGG ATGATTAGCT TCGAATACTT CCTCAGGTAC    420
ATAAGATTCC GTTACTAAAA GCACCGCTGT GGCAGCTGCA GCTTCAGCAC CTTCTTCATT    480
TACTTCAATG AAAGCTTTTT GAATTACTTT AGAAATATAT AACATCTCAT CAGATCCTTC    540
AAGCAATCCT TTGAAATCAG CTTTTCCAGG AACAAACATA TCAGACATAC CCAACTTTTT    600
CAGAGGATCA TTCAAATTAA TTTCAGATTC AATCTTGAAT TTAGGCAGAT CCAAAATAAC    660
TTCAACAGAG TACATGCGTT GAGTCAAGTT TTGCAAGTCA ACATTTTGTA ATTTTTCTTC    720
AAGAGCGGGG AGACCAGTTT TGCTGTTTGG CAAAATGATT AACATGGCCA AATCTGAGTT    780
CCTGTAGGGC AATTCTACAG CCTTGGCATC TAATTCTTCA AATTCTCCAT AACGGAATTT    840
ATCCTTAATG TGCATCATTC GTACATTCTT TGTCTCTGTT TCAGTAACAT AGAAAGGTTT    900
GTCTTGAGTG TTTTCCTTCT TGAATTGTTT CTCCCAAAGA CCCTTGAAGT ACAATGCATT    960
GACAAGAACC ATTCTTGAAT CCTGGTCTAG ATCACCGGCT TTGATCAAAT CATGAATTTT   1020
GTCATGAGTT TTTTCTTCAA CCCAAGTGTT GATAACTTTA GCGCTTTCAG CATTTTGGGC   1080
AAAGTTCAAG TTTTCTGCTC CAGCTAAGAA TTTGTTGGTG GCAACTTCTT TGAAGGTGGG   1140
TTTCAATGTA TAGCCTTCCA TAACGTAAAC TTTGTTGGCA ATTTCCAGAG TTACACCTTT   1200
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TTGTGTATTA AGAGTGTTCA TCAATGCATG GTAGTCATCT TGAATTTTTT CTTTTGATTG 1260
AGGCTGACGT AAACCAGCAG CTATTTGTGT GGCAGTATTA CCACCAGCTC CCATTGACAC 1320
CAGGGATAGA ACAGTTTGTA CAGACAATGG GGACATGATG AGATTGTCTT TGTTGCCAGA 1380
AGCAACCGTA TTGTACAGGC TTCCAGCAAA CTGGTTAATA CTTGTAGACA ATTCCTGGGG 1440
ATCCGCCATT GTTGAAATTG GTATTAACAC TGATACAAAA AGAAACACAA GTCGTGCGTG 1500
TTGAACTATC GCGTCAAACT GAGGACGCGG CATCAAAACT CTAGATATTA GAATCGTTTG 1560
TGAGTCATAT TGTATAATAT AGAAATACTA GGAATGTTTG AATAACACAC TATATACATT 1620
CAAACATTTG GCTTCGCGGA ACAACACACA TGAATCTGTT TTATATTTCT GTCGTCCTTG 1680
GAATCACACA GTTTCCAAAA ATTAGCTTCA TTTTTATATT TGTGTTTAAT TTATTTTGAA 1740
CATGATGTCA TTTGAATGAT AGTTATTGAA TTGATTTGTA TGTATTTTTG GAGATACTGA 1800
TTTTAATATT CTAAATGCGT AATTTGACTT TGCACAAT                         1838
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1260 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
ATGCCGCGTC CTCAGTTTGA CGCGATAGTT CAACACGCAC GACTTGTGTT TCTTTTTGTA   60
TCAGTGTTAA TACCAATTTC AACAATGGCG GATCCCCAGG AATTGTCTAC AAGTATTAAC  120
CAGTTTGCTG GAAGCCTGTA CAATACGGTT GCTTCTGGCA ACAAAGACAA TCTCATCATG  180
TCCCCATTGT CTGTACAAAC TGTTCTATCC CTGGTGTCAA TGGGAGCTGG TGGTAATACT  240
GCCACACAAA TAGCTGCTGG TTTACGTCAG CCTCAATCAA AAGAAAAAAT TCAAGATGAC  300
TACCATGCAT TGATGAACAC TCTTAATACA CAAAAAGGTG TAACTCTGGA AATTGCCAAC  360
AAAGTTTACG TTATGGAAGG CTATACATTG AAACCCACCT TCAAAGAAGT TGCCACCAAC  420
AAATTCTTAG CTGGAGCAGA AAACTTGAAC TTTGCCCAAA ATGCTGAAAG CGCTAAAGTT  480
ATCAACACTT GGGTTGAAGA AAAAACTCAT GACAAAATTC ATGATTTGAT CAAAGCCGGT  540
GATCTAGACC AGGATTCAAG AATGGTTCTT GTCAATGCAT TGTACTTCAA GGGTCTTTGG  600
GAGAAACAAT TCAAGAAGGA AAACACTCAA GACAAACCTT TCTATGTTAC TGAAACAGAG  660
ACAAAGAATG TACGAATGAT GCACATTAAG GATAAATTCC GTTATGGAGA ATTTGAAGAA  720
TTAGATGCCA AGGCTGTAGA ATTGCCCTAC AGGAACTCAG ATTTGGCCAT GTTAATCATT  780
TTGCCAAACA GCAAAACTGG TCTCCCCGCT CTTGAAGAAA AATTACAAAA TGTTGACTTG  840
CAAAACTTGA CTCAACGCAT GTACTCTGTT GAAGTTATTT TGGATCTGCC TAAATTCAAG  900
ATTGAATCTG AAATTAATTT GAATGATCCT CTGAAAAAGT TGGGTATGTC TGATATGTTT  960
GTTCCTGGAA AAGCTGATTT CAAAGGATTG CTTGAAGGAT CTGATGAGAT GTTATATATT 1020
TCTAAAGTAA TTCAAAAAGC TTTCATTGAA GTAAATGAAG AAGGTGCTGA AGCTGCAGCT 1080
GCCACAGCGG TGCTTTTAGT AACGGAATCT TATGTACCTG AGGAAGTATT CGAAGCTAAT 1140
CATCCCTTTT ATTTTGCACT CTATAAATCT GCACAAAATC CAGTAGAATC TGAAAATGAA 1200
AGCTCTGAAA ATGAAAACCC TGAAAATGTT GAAGTACTAT TCTCTGGGAG ATTTACCAAT 1260
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1260 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ATTGGTAAAT CTCCCAGAGA ATAGTACTTC AACATTTTCA GGGTTTTCAT TTTCAGAGCT   60
TTCATTTTCA GATTCTACTG GATTTTGTGC AGATTTATAG AGTGCAAAAT AAAAGGGATG  120
ATTAGCTTCG AATACTTCCT CAGGTACATA AGATTCCGTT ACTAAAAGCA CCGCTGTGGC  180
AGCTGCAGCT TCAGCACCTT CTTCATTTAC TTCAATGAAA GCTTTTTGAA TTACTTTAGA  240
```

```
AATATATAAC ATCTCATCAG ATCCTTCAAG CAATCCTTTG AAATCAGCTT TTCCAGGAAC    300
AAACATATCA GACATACCCA ACTTTTTCAG AGGATCATTC AAATTAATTT CAGATTCAAT    360
CTTGAATTTA GGCAGATCCA AAATAACTTC AACAGAGTAC ATGCGTTGAG TCAAGTTTTG    420
CAAGTCAACA TTTTGTAATT TTTCTTCAAG AGCGGGGAGA CCAGTTTTGC TGTTTGGCAA    480
AATGATTAAC ATGGCCAAAT CTGAGTTCCT GTAGGGCAAT TCTACAGCCT TGGCATCTAA    540
TTCTTCAAAT TCTCCATAAC GGAATTTATC CTTAATGTGC ATCATTCGTA CATTCTTTGT    600
CTCTGTTTCA GTAACATAGA AAGGTTTGTC TTGAGTGTTT TCCTTCTTGA ATTGTTTCTC    660
CCAAAGACCC TTGAAGTACA ATGCATTGAC AAGAACCATT CTTGAATCCT GGTCTAGATC    720
ACCGGCTTTG ATCAAATCAT GAATTTTGTC ATGAGTTTTT TCTTCAACCC AAGTGTTGAT    780
AACTTTAGCG CTTTCAGCAT TTTGGGCAAA GTTCAAGTTT TCTGCTCCAG CTAAGAATTT    840
GTTGGTGGCA ACTTCTTTGA AGGTGGGTTT CAATGTATAG CCTTCCATAA CGTAAACTTT    900
GTTGGCAATT TCCAGAGTTA CACCTTTTTG TGTATTAAGA GTGTTCATCA ATGCATGGTA    960
GTCATCTTGA ATTTTTTCTT TTGATTGAGG CTGACGTAAA CCAGCAGCTA TTTGTGTGGC   1020
AGTATTACCA CCAGCTCCCA TTGACACCAG GGATAGAACA GTTTGTACAG ACAATGGGGA   1080
CATGATGAGA TTGTCTTTGT TGCCAGAAGC AACCGTATTG TACAGGCTTC CAGCAAACTG   1140
GTTAATACTT GTAGACAATT CCTGGGGATC CGCCATTGTT GAAATTGGTA TTAACACTGA   1200
TACAAAAAGA AACACAAGTC GTGCGTGTTG AACTATCGCG TCAAACTGAG GACGCGGCAT   1260
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 390 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu
 1               5                  10                  15

Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
            20                  25                  30

Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly
        35                  40                  45

Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys
    50                  55                  60

Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr
65                  70                  75                  80

Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu
                85                  90                  95

Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe
            100                 105                 110

Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala
        115                 120                 125

Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His
    130                 135                 140

Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu
145                 150                 155                 160

Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys
                165                 170                 175
```

Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys
180 185 190

Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe
195 200 205

Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp
210 215 220

Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala
225 230 235 240

Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg
245 250 255

Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu
260 265 270

Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp
275 280 285

Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser
290 295 300

Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu
305 310 315 320

Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Val Leu Leu
325 330 335

Val Thr Glu Ser Tyr Val Pro Glu Glu Val Phe Glu Ala Asn His Pro
340 345 350

Phe Tyr Phe Ala Leu Tyr Lys Ser Ala Gln Asn Pro Val Glu Ser Glu
355 360 365

Asn Glu Ser Ser Glu Asn Glu Asn Pro Glu Asn Val Glu Val Leu Phe
370 375 380

Ser Gly Arg Phe Thr Asn
385 390

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1414 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..1180

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

A CGA CTT GTG TTT CTT TTT GTA TCA GTG TTA ATA CCA ATT TCA ACA 46
Arg Leu Val Phe Leu Phe Val Ser Val Leu Ile Pro Ile Ser Thr
1 5 10 15

```
ATG GCG GAT CCC CAG GAA TTG TCT ACA AGT ATT AAC CAG TTT GCT GGA     94
Met Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly
                20                  25                  30

AGC CTG TAC AAT ACG GTT GCT TCT GGC AAC AAA GAC AAT CTC ATC ATG    142
Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met
            35                  40                  45

TCC CCA TTG TCT GTA CAA ACT GTT CTA TCC CTG GTG TCA ATG GGA GCT    190
Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala
        50                  55                  60

GGT GGT AAT ACT GCC ACA CAA ATA GCT GCT GGT TTA CGT CAG CCT CAA    238
Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln
    65                  70                  75

TCA AAA GAA AAA ATT CAA GAT GAC TAC CAT GCA TTG ATG AAC ACT CTT    286
Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu
80                  85                  90                  95

AAT ACA CAA AAA GGT GTA ACT CTG GAA ATT GCC AAC AAA GTT TAC GTT    334
Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val
                100                 105                 110

ATG GAA GGC TAT ACA TTG AAA CCC ACC TTC AAA GAA GTT GCC ACC AAC    382
Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn
            115                 120                 125

AAA TTC TTA GCT GGA GCA GAA AAC TTG AAC TTT GCC CAA AAT GCT GAA    430
Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu
        130                 135                 140

AGC GCT AAA GTT ATC AAC ACT TGG GTT GAA GAA AAA ACT CAT GAC AAA    478
Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys
    145                 150                 155

ATT CAT GAT TTG ATC AAA GCC GGT GAT CTA GAC CAG GAT TCA AGA ATG    526
Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met
160                 165                 170                 175

GTT CTT GTC AAT GCA TTG TAC TTC AAG GGT CTT TGG GAG AAA CAA TTC    574
Val Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe
                180                 185                 190

AAG AAG GAA AAC ACT CAA GAC AAA CCT TTC TAT GTT ACT GAA ACA GAG    622
Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu
            195                 200                 205

ACA AAG AAT GTA CGA ATG ATG CAC ATT AAG GAT AAA TTC CGT TAT GGA    670
Thr Lys Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly
        210                 215                 220

GAA TTT GAA GAA TTA GAT GCC AAG GCT GTA GAA TTG CCC TAC AGG AAC    718
Glu Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn
    225                 230                 235

TCA GAT TTG GCC ATG TTA ATC ATT TTG CCA AAC AGC AAA ACT GGT CTC    766
Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu
240                 245                 250                 255
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CCC GCT CTT GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT      814
Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr
                260                 265                 270

CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC AAG      862
Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys
            275                 280                 285

ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG TTG GGT ATG      910
Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met
        290                 295                 300

TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC AAA GGA TTG CTT GAA      958
Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu
    305                 310                 315

GGA TCT GAT GAG ATG TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC     1006
Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe
320                 325                 330                 335

ATT GAA GTA AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GGC GTG     1054
Ile Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Val
                340                 345                 350

ATG TTA ATG ATG CGT TGT ATG CCA ATG ATG CCA ATG GCC TTC AAT GCT     1102
Met Leu Met Met Arg Cys Met Pro Met Met Pro Met Ala Phe Asn Ala
            355                 360                 365

GAG CAT CCA TTC CTG TAC TTC TTA CAC AGC AAA AAT TCT GTT CTA TTC     1150
Glu His Pro Phe Leu Tyr Phe Leu His Ser Lys Asn Ser Val Leu Phe
        370                 375                 380

AAT GGT CGT CTT GTT AAA CCA ACA ACT GAA TAA AAGCCAAATG CACTTCACTA   1203
Asn Gly Arg Leu Val Lys Pro Thr Thr Glu
    385                 390

ATATTTTTTA ATTGCTTACT GAAACAGTGC CTGTAGAACA TTGTGTTCAA TTTATATTTG   1263
TCAGCTTTAA GTATTCAGTA TTTTTTATCA TCACTATTTC AGTGGTGGAT CTTAAGTACA   1323
AATTTATTGT TATGATATAT ATTTATTTTT TGTGAATATT TTTTTAACAA ATTTTGATAA   1383
AAAACATAAG ACTAAAAAAA AAAAAAAAAA A                                  1414
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 393 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Arg Leu Val Phe Leu Phe Val Ser Val Leu Ile Pro Ile Ser Thr Met
1               5                   10                  15

Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser
            20                  25                  30

Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser
        35                  40                  45
```

```
Pro Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly
     50                  55                  60

Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser
 65                  70                  75                  80

Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn
                 85                  90                  95

Thr Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met
            100                 105                 110

Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys
        115                 120                 125

Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser
    130                 135                 140

Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile
145                 150                 155                 160

His Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val
                165                 170                 175

Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys
            180                 185                 190

Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr
        195                 200                 205

Lys Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu
    210                 215                 220

Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser
225                 230                 235                 240

Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro
                245                 250                 255

Ala Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
            260                 265                 270

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile
        275                 280                 285

Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser
    290                 295                 300

Asp Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly
305                 310                 315                 320

Ser Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile
                325                 330                 335

Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Val Met
            340                 345                 350

Leu Met Met Arg Cys Met Pro Met Met Pro Met Ala Phe Asn Ala Glu
        355                 360                 365

His Pro Phe Leu Tyr Phe Leu His Ser Lys Asn Ser Val Leu Phe Asn
    370                 375                 380
```

Gly Arg Leu Val Lys Pro Thr Thr Glu
385 390

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1414 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
TTTTTTTTTT TTTTTTTTAG TCTTATGTTT TTTATCAAAA TTTGTTAAAA AAATATTCAC    60
AAAAAATAAA TATATATCAT AACAATAAAT TTGTACTTAA GATCCACCAC TGAAATAGTG   120
ATGATAAAAA ATACTGAATA CTTAAAGCTG ACAAATATAA ATTGAACACA ATGTTCTACA   180
GGCACTGTTT CAGTAAGCAA TTAAAAAATA TTAGTGAAGT GCATTTGGCT TTTATTCAGT   240
TGTTGGTTTA ACAAGACGAC CATTGAATAG AACAGAATTT TTGCTGTGTA AGAAGTACAG   300
GAATGGATGC TCAGCATTGA AGGCCATTGG CATCATTGGC ATACAACGCA TCATTAACAT   360
CACGCCTGTG GCAGCTGCAG CTTCAGCACC TTCTTCATTT ACTTCAATGA AAGCTTTTTG   420
AATTACTTTA GAAATATATA ACATCTCATC AGATCCTTCA AGCAATCCTT TGAAATCAGC   480
TTTTCCAGGA ACAAACATAT CAGACATACC CAACTTTTTC AGAGGATCAT TCAAATTAAT   540
TTCAGATTCA ATCTTGAATT TAGGCAGATC CAAAATAACT TCAACAGAGT ACATGCGTTG   600
AGTCAAGTTT TGCAAGTCAA CATTTTGTAA TTTTTCTTCA AGAGCGGGGA GACCAGTTTT   660
GCTGTTTGGC AAAATGATTA ACATGGCCAA ATCTGAGTTC CTGTAGGGCA ATTCTACAGC   720
CTTGGCATCT AATTCTTCAA ATTCTCCATA ACGGAATTTA TCCTTAATGT GCATCATTCG   780
TACATTCTTT GTCTCTGTTT CAGTAACATA GAAAGGTTTG TCTTGAGTGT TTTCCTTCTT   840
GAATTGTTTC TCCCAAAGAC CCTTGAAGTA CAATGCATTG ACAAGAACCA TTCTTGAATC   900
CTGGTCTAGA TCACCGGCTT TGATCAAATC ATGAATTTTG TCATGAGTTT TTTCTTCAAC   960
CCAAGTGTTG ATAACTTTAG CGCTTTCAGC ATTTTGGGCA AAGTTCAAGT TTTCTGCTCC  1020
AGCTAAGAAT TTGTTGGTGG CAACTTCTTT GAAGGTGGGT TTCAATGTAT AGCCTTCCAT  1080
AACGTAAACT TTGTTGGCAA TTTCCAGAGT TACACCTTTT TGTGTATTAA GAGTGTTCAT  1140
CAATGCATGG TAGTCATCTT GAATTTTTTC TTTTGATTGA GGCTGACGTA AACCAGCAGC  1200
TATTTGTGTG GCAGTATTAC CACCAGCTCC CATTGACACC AGGGATAGAA CAGTTTGTAC  1260
AGACAATGGG GACATGATGA GATTGTCTTT GTTGCCAGAA GCAACCGTAT TGTACAGGCT  1320
TCCAGCAAAC TGGTTAATAC TTGTAGACAA TTCCTGGGGA TCCGCCATTG TTGAAATTGG  1380
TATTAACACT GATACAAAAA GAAACACAAG TCGT                              1414
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1179 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
CGACTTGTGT TTCTTTTTGT ATCAGTGTTA ATACCAATTT CAACAATGGC GGATCCCCAG    60
GAATTGTCTA CAAGTATTAA CCAGTTTGCT GGAAGCCTGT ACAATACGGT TGCTTCTGGC   120
AACAAAGACA ATCTCATCAT GTCCCCATTG TCTGTACAAA CTGTTCTATC CCTGGTGTCA   180
ATGGGAGCTG GTGGTAATAC TGCCACACAA ATAGCTGCTG GTTTACGTCA GCCTCAATCA   240
AAAGAAAAAA TTCAAGATGA CTACCATGCA TTGATGAACA CTCTTAATAC ACAAAAAGGT   300
GTAACTCTGG AAATTGCCAA CAAAGTTTAC GTTATGGAAG GCTATACATT GAAACCCACC   360
TTCAAAGAAG TTGCCACCAA CAAATTCTTA GCTGGAGCAG AAAACTTGAA CTTTGCCCAA   420
AATGCTGAAA GCGCTAAAGT TATCAACACT TGGGTTGAAG AAAAAACTCA TGACAAAATT   480
CATGATTTGA TCAAAGCCGG TGATCTAGAC CAGGATTCAA GAATGGTTCT TGTCAATGCA   540
TTGTACTTCA AGGGTCTTTG GGAGAAACAA TTCAAGAAGG AAAACACTCA AGACAAACCT   600
```

```
TTCTATGTTA CTGAAACAGA GACAAAGAAT GTACGAATGA TGCACATTAA GGATAAATTC    660
CGTTATGGAG AATTTGAAGA ATTAGATGCC AAGGCTGTAG AATTGCCCTA CAGGAACTCA    720
GATTTGGCCA TGTTAATCAT TTTGCCAAAC AGCAAAACTG GTCTCCCCGC TCTTGAAGAA    780
AAATTACAAA ATGTTGACTT GCAAAACTTG ACTCAACGCA TGTACTCTGT TGAAGTTATT    840
TTGGATCTGC CTAAATTCAA GATTGAATCT GAAATTAATT TGAATGATCC TCTGAAAAAG    900
TTGGGTATGT CTGATATGTT TGTTCCTGGA AAAGCTGATT TCAAAGGATT GCTTGAAGGA    960
TCTGATGAGA TGTTATATAT TTCTAAAGTA ATTCAAAAAG CTTTCATTGA AGTAAATGAA   1020
GAAGGTGCTG AAGCTGCAGC TGCCACAGGC GTGATGTTAA TGATGCGTTG TATGCCAATG   1080
ATGCCAATGG CCTTCAATGC TGAGCATCCA TTCCTGTACT TCTTACACAG CAAAAATTCT   1140
GTTCTATTCA ATGGTCGTCT TGTTAAACCA ACAACTGAA                          1179
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1179 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
TTCAGTTGTT GGTTTAACAA GACGACCATT GAATAGAACA GAATTTTTGC TGTGTAAGAA     60
GTACAGGAAT GGATGCTCAG CATTGAAGGC CATTGGCATC ATTGGCATAC AACGCATCAT    120
TAACATCACG CCTGTGGCAG CTGCAGCTTC AGCACCTTCT TCATTTACTT CAATGAAAGC    180
TTTTTGAATT ACTTTAGAAA TATATAACAT CTCATCAGAT CCTTCAAGCA ATCCTTTGAA    240
ATCAGCTTTT CCAGGAACAA ACATATCAGA CATACCCAAC TTTTTCAGAG GATCATTCAA    300
ATTAATTTCA GATTCAATCT TGAATTTAGG CAGATCCAAA ATAACTTCAA CAGAGTACAT    360
GCGTTGAGTC AAGTTTTGCA AGTCAACATT TTGTAATTTT TCTTCAAGAG CGGGGAGACC    420
AGTTTTGCTG TTTGGCAAAA TGATTAACAT GGCCAAATCT GAGTTCCTGT AGGGCAATTC    480
TACAGCCTTG GCATCTAATT CTTCAAATTC TCCATAACGG AATTTATCCT TAATGTGCAT    540
CATTCGTACA TTCTTTGTCT CTGTTTCAGT AACATAGAAA GGTTTGTCTT GAGTGTTTTC    600
CTTCTTGAAT TGTTTCTCCC AAAGACCCTT GAAGTACAAT GCATTGACAA GAACCATTCT    660
TGAATCCTGG TCTAGATCAC CGGCTTTGAT CAAATCATGA ATTTTGTCAT GAGTTTTTTC    720
TTCAACCCAA GTGTTGATAA CTTTAGCGCT TTCAGCATTT TGGGCAAAGT TCAAGTTTTC    780
TGCTCCAGCT AAGAATTTGT TGGTGGCAAC TTCTTTGAAG GTGGGTTTCA ATGTATAGCC    840
TTCCATAACG TAAACTTTGT TGGCAATTTC CAGAGTTACA CCTTTTTGTG TATTAAGAGT    900
GTTCATCAAT GCATGGTAGT CATCTTGAAT TTTTTCTTTT GATTGAGGCT GACGTAAACC    960
AGCAGCTATT TGTGTGGCAG TATTACCACC AGCTCCCATT GACACCAGGG ATAGAACAGT   1020
TTGTACAGAC AATGGGGACA TGATGAGATT GTCTTTGTTG CCAGAAGCAA CCGTATTGTA   1080
CAGGCTTCCA GCAAACTGGT TAATACTTGT AGACAATTCC TGGGGATCCG CCATTGTTGA   1140
AATTGGTATT AACACTGATA CAAAAAGAAA CACAAGTCG                          1179
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 376 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu
 1               5                  10                  15

Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
            20                  25                  30
```

Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly
35 40 45

Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys
50 55 60

Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr
65 70 75 80

Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu
85 90 95

Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe
100 105 110

Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala
115 120 125

Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His
130 135 140

Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu
145 150 155 160

Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys
165 170 175

Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys
180 185 190

Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe
195 200 205

Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp
210 215 220

Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala
225 230 235 240

Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg
245 250 255

Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu
260 265 270

Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp
275 280 285

Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser
290 295 300

Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu
305 310 315 320

Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Val Met Leu
325 330 335

Met Met Arg Cys Met Pro Met Met Pro Met Ala Phe Asn Ala Glu His
340 345 350

Pro Phe Leu Tyr Phe Leu His Ser Lys Asn Ser Val Leu Phe Asn Gly
355 360 365

```
Arg Leu Val Lys Pro Thr Thr Glu
    370                 375

(2)   INFORMATION FOR SEQ ID NO:25:

      (i)    SEQUENCE CHARACTERISTICS:
             (A)  LENGTH:  1492 nucleotides
             (B)  TYPE:  nucleic acid
             (C)  STRANDEDNESS:  single
             (D)  TOPOLOGY:  linear

      (ii)   MOLECULE TYPE:  cDNA

      (ix)   FEATURE:
             (A)  NAME/KEY:  CDS
             (B)  LOCATION:  3..1196

      (xi)   SEQUENCE DESCRIPTION:  SEQ ID NO:25:

CG ATA GTT CAA CAC GCA CGA CTT GTG TTT CTT TTT GTA TCA GTG TTA        47
   Ile Val Gln His Ala Arg Leu Val Phe Leu Phe Val Ser Val Leu
    1               5                  10                  15

ATA CCA ATT TCA ACA ATG GCG GAT CCC CAG GAA TTG TCT ACA AGT ATT       95
Ile Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile
                20                  25                  30

AAC CAG TTT GCT GGA AGC CTG TAC AAT ACG GTT GCT TCT GGC AAC AAA      143
Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys
            35                  40                  45

GAC AAT CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT CTA TCC CTG      191
Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu
        50                  55                  60

GTG TCA ATG GGA GCT GGT GGT AAT ACT GCC ACA CAA ATA GCT GCT GGT      239
Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly
    65                  70                  75

TTA CGT CAG CCT CAA TCA AAA GAA AAA ATT CAA GAT GAC TAC CAC GCA      287
Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala
 80                  85                  90                  95

TTG ATG AAC ACT CTT AAT ACA CAA AAA GGT GTA ACT CTG GAA ATT GCC      335
Leu Met Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala
                100                 105                 110

AAT AAA GTT TAT GTT ATG GAA GGC TAT ACA TTA AAA CCC ACC TTC AAA      383
Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys
            115                 120                 125

GAA GTT GCC ACC AAC AAA TTC TTA GCT GGA GCA GAA AAC TTG AAC TTT      431
Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe
        130                 135                 140

GCC CAA AAT GCT GAA AGC GCT AAA GTT ATC AAC ACT TGG GTT GAA GAA      479
Ala Gln Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu
    145                 150                 155

AAA ACT CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT GAT CTA GAC      527
Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp
160                 165                 170                 175
```

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CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC TTC AAG GGT CTT      575
Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu
                180                 185                 190

TGG GAG AAA CAA TTC AAG AAG GAA AAC ACC CAA GAC AAA CCT TTC TAT      623
Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr
            195                 200                 205

GTT ACT GAA ACA GAG ACA AAG AAT GTA CGA ATG ATG CAC ATT AAG GAT      671
Val Thr Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp
        210                 215                 220

AAA TTC CGT TAT GGA GAA TTT GAA GAA TTA GAT GCC AAG GCT GTA GAA      719
Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala Val Glu
    225                 230                 235

TTG CCC TAC AGG AAC TCA GAT TTG GCC ATG TTA ATC ATT TTG CCA AAC      767
Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn
240                 245                 250                 255

AGC AAA ACT GGT CTC CCC ACT CTT GAA GAA AAA TTA CAA AAT GTT GAT      815
Ser Lys Thr Gly Leu Pro Thr Leu Glu Glu Lys Leu Gln Asn Val Asp
                260                 265                 270

TTG CAA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT      863
Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
            275                 280                 285

CTG CCT AAA TTC AAA ATT GAG TCT GAA ATT AAT TTG AAT GAT CCT CTG      911
Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu
        290                 295                 300

AAA AAG TTG GGT ATG TCT GAT ATG TTC ATG CCT GGA AAA GCT GAT TTC      959
Lys Lys Leu Gly Met Ser Asp Met Phe Met Pro Gly Lys Ala Asp Phe
    305                 310                 315

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT AAA GTA     1007
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val
320                 325                 330                 335

ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT GCT GAA GCT GCA     1055
Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu Ala Ala
                340                 345                 350

GCT GCC ACA GGC GTG ATG TTA ATG ATG CGT TGT ATG CCA ATG ATG CCA     1103
Ala Ala Thr Gly Val Met Leu Met Met Arg Cys Met Pro Met Met Pro
            355                 360                 365

ATG GCC TTC AAT GCT GAG CAT CCA TTC CTG TAC TTC TTA CAC AGC AAA     1151
Met Ala Phe Asn Ala Glu His Pro Phe Leu Tyr Phe Leu His Ser Lys
        370                 375                 380

AAT TCT GTT CTA TTC AAT GGT CGT CTT GTT AAA CCA ACA ACT GAA TAA     1199
Asn Ser Val Leu Phe Asn Gly Arg Leu Val Lys Pro Thr Thr Glu
    385                 390                 395

AAGCCAAATG CACTTCACTA ATATTTTTTA ATTGCTTACT GAAACAGTGC CTGTAGAACA   1259
TTGTGTTCAA TTTATATTTG TCAGCTTTAA GTATTCAGTA TTTTTTATCA TCACTATTTC   1319
AGTGGTGGAT CTTAAGTACA AATTTATTGT TATGATATAT ATTTATTTTT TGTGAATATT   1379
TTTTTAACAA ATTTTGATAA AAAACATAAG ACTAAAAATA AAAGAAAAAT TAAAATTTAT   1439
GTATAATTGT TGTATACTAA ATTATATCTT TAAGAAAAAA AAAAAAAAAA AAA          1492
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 398 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Ile Val Gln His Ala Arg Leu Val Phe Leu Phe Val Ser Val Leu Ile
 1               5                  10                  15

Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn
            20                  25                  30

Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp
        35                  40                  45

Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu Val
    50                  55                  60

Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu
65                  70                  75                  80

Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu
                85                  90                  95

Met Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala Asn
            100                 105                 110

Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu
        115                 120                 125

Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala
    130                 135                 140

Gln Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys
145                 150                 155                 160

Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln
                165                 170                 175

Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp
            180                 185                 190

Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val
        195                 200                 205

Thr Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp Lys
    210                 215                 220

Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu
225                 230                 235                 240

Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser
                245                 250                 255

Lys Thr Gly Leu Pro Thr Leu Glu Glu Lys Leu Gln Asn Val Asp Leu
            260                 265                 270
```

```
Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu
        275                 280                 285

Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys
    290                 295                 300

Lys Leu Gly Met Ser Asp Met Phe Met Pro Gly Lys Ala Asp Phe Lys
305                 310                 315                 320

Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val Ile
                325                 330                 335

Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala
            340                 345                 350

Ala Thr Gly Val Met Leu Met Met Arg Cys Met Pro Met Met Pro Met
        355                 360                 365

Ala Phe Asn Ala Glu His Pro Phe Leu Tyr Phe Leu His Ser Lys Asn
    370                 375                 380

Ser Val Leu Phe Asn Gly Arg Leu Val Lys Pro Thr Thr Glu
385                 390                 395
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1492 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
TTTTTTTTTT TTTTTTTTTC TTAAAGATAT AATTTAGTAT ACAACAATTA TACATAAATT     60
TTAATTTTTC TTTTATTTTT AGTCTTATGT TTTTTATCAA AATTTGTTAA AAAAATATTC    120
ACAAAAAATA AATATATATC ATAACAATAA ATTTGTACTT AAGATCCACC ACTGAAATAG    180
TGATGATAAA AAATACTGAA TACTTAAAGC TGACAAATAT AAATTGAACA CAATGTTCTA    240
CAGGCACTGT TTCAGTAAGC AATTAAAAAA TATTAGTGAA GTGCATTTGG CTTTTATTCA    300
GTTGTTGGTT TAACAAGACG ACCATTGAAT AGAACAGAAT TTTTGCTGTG TAAGAAGTAC    360
AGGAATGGAT GCTCAGCATT GAAGGCCATT GGCATCATTG GCATACAACG CATCATTAAC    420
ATCACGCCTG TGGCAGCTGC AGCTTCAGCA CCTTCTTCAT TTACTTCAAT GAAAGCTTTT    480
TGAATTACTT TAGAAATATA TAACATCTCA TCAGATCCTT CAAGCAATCC TTTGAAATCA    540
GCTTTTCCAG GCATGAACAT ATCAGACATA CCCAACTTTT TCAGAGGATC ATTCAAATTA    600
ATTTCAGACT CAATTTTGAA TTTAGGCAGA TCCAAAATAA CTTCAACAGA GTACATGCGT    660
TGAGTCAAGT TTTGCAAATC AACATTTTGT AATTTTTCTT CAAGAGTGGG GAGACCAGTT    720
TTGCTGTTTG GCAAAATGAT TAACATGGCC AAATCTGAGT TCCTGTAGGG CAATTCTACA    780
GCCTTGGCAT CTAATTCTTC AAATTCTCCA TAACGGAATT TATCCTTAAT GTGCATCATT    840
CGTACATTCT TTGTCTCTGT TTCAGTAACA TAGAAAGGTT TGTCTTGGGT GTTTTCCTTC    900
TTGAATTGTT TCTCCCAAAG ACCCTTGAAG TACAATGCAT TGACAAGAAC CATTCTTGAA    960
TCCTGGTCTA GATCACCGGC TTTGATCAAA TCATGAATTT TGTCATGAGT TTTTTCTTCA   1020
ACCCAAGTGT TGATAACTTT AGCGCTTTCA GCATTTTGGG CAAAGTTCAA GTTTTCTGCT   1080
CCAGCTAAGA ATTTGTTGGT GGCAACTTCT TTGAAGGTGG GTTTTAATGT ATAGCCTTCC   1140
ATAACATAAA CTTTATTGGC AATTTCCAGA GTTACACCTT TTTGTGTATT AAGAGTGTTC   1200
ATCAATGCGT GGTAGTCATC TTGAATTTTT TCTTTTGATT GAGGCTGACG TAAACCAGCA   1260
GCTATTTGTG TGGCAGTATT ACCACCAGCT CCCATTGACA CCAGGGATAG AACAGTTTGT   1320
ACAGACAATG GGGACATGAT GAGATTGTCT TTGTTGCCAG AAGCAACCGT ATTGTACAGG   1380
CTTCCAGCAA ACTGGTTAAT ACTTGTAGAC AATTCCTGGG GATCCGCCAT TGTTGAAATT   1440
GGTATTAACA CTGATACAAA AAGAAACACA AGTCGTGCGT GTTGAACTAT CG           1492
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1194 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
ATAGTTCAAC ACGCACGACT TGTGTTTCTT TTTGTATCAG TGTTAATACC AATTTCAACA    60
ATGGCGGATC CCCAGGAATT GTCTACAAGT ATTAACCAGT TTGCTGGAAG CCTGTACAAT   120
ACGGTTGCTT CTGGCAACAA AGACAATCTC ATCATGTCCC CATTGTCTGT ACAAACTGTT   180
CTATCCCTGG TGTCAATGGG AGCTGGTGGT AATACTGCCA CACAAATAGC TGCTGGTTTA   240
CGTCAGCCTC AATCAAAAGA AAAAATTCAA GATGACTACC ACGCATTGAT GAACACTCTT   300
AATACACAAA AAGGTGTAAC TCTGGAAATT GCCAATAAAG TTTATGTTAT GGAAGGCTAT   360
ACATTAAAAC CCACCTTCAA AGAAGTTGCC ACCAACAAAT TCTTAGCTGG AGCAGAAAAC   420
TTGAACTTTG CCCAAAATGC TGAAAGCGCT AAAGTTATCA ACACTTGGGT TGAAGAAAAA   480
ACTCATGACA AAATTCATGA TTTGATCAAA GCCGGTGATC TAGACCAGGA TTCAAGAATG   540
GTTCTTGTCA ATGCATTGTA CTTCAAGGGT CTTTGGGAGA AACAATTCAA GAAGGAAAAC   600
ACCCAAGACA AACCTTTCTA TGTTACTGAA ACAGAGACAA AGAATGTACG AATGATGCAC   660
ATTAAGGATA AATTCCGTTA TGGAGAATTT GAAGAATTAG ATGCCAAGGC TGTAGAATTG   720
CCCTACAGGA ACTCAGATTT GGCCATGTTA ATCATTTTGC CAAACAGCAA AACTGGTCTC   780
CCCACTCTTG AAGAAAAATT ACAAAATGTT GATTTGCAAA ACTTGACTCA ACGCATGTAC   840
TCTGTTGAAG TTATTTTGGA TCTGCCTAAA TTCAAAATTG AGTCTGAAAT TAATTTGAAT   900
GATCCTCTGA AAAAGTTGGG TATGTCTGAT ATGTTCATGC CTGGAAAAGC TGATTTCAAA   960
GGATTGCTTG AAGGATCTGA TGAGATGTTA TATATTTCTA AAGTAATTCA AAAAGCTTTC  1020
ATTGAAGTAA ATGAAGAAGG TGCTGAAGCT GCAGCTGCCA CAGGCGTGAT GTTAATGATG  1080
CGTTGTATGC CAATGATGCC AATGGCCTTC AATGCTGAGC ATCCATTCCT GTACTTCTTA  1140
CACAGCAAAA ATTCTGTTCT ATTCAATGGT CGTCTTGTTA AACCAACAAC TGAA        1194
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1194 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
TTCAGTTGTT GGTTTAACAA GACGACCATT GAATAGAACA GAATTTTTGC TGTGTAAGAA    60
GTACAGGAAT GGATGCTCAG CATTGAAGGC CATTGGCATC ATTGGCATAC AACGCATCAT   120
TAACATCACG CCTGTGGCAG CTGCAGCTTC AGCACCTTCT TCATTTACTT CAATGAAAGC   180
TTTTTGAATT ACTTTAGAAA TATATAACAT CTCATCAGAT CCTTCAAGCA ATCCTTTGAA   240
ATCAGCTTTT CCAGGCATGA ACATATCAGA CATACCCAAC TTTTTCAGAG GATCATTCAA   300
ATTAATTTCA GACTCAATTT TGAATTTAGG CAGATCCAAA ATAACTTCAA CAGAGTACAT   360
GCGTTGAGTC AAGTTTTGCA AATCAACATT TTGTAATTTT TCTTCAAGAG TGGGGAGACC   420
AGTTTTGCTG TTTGGCAAAA TGATTAACAT GGCCAAATCT GAGTTCCTGT AGGGCAATTC   480
TACAGCCTTG GCATCTAATT CTTCAAATTC TCCATAACGG AATTTATCCT TAATGTGCAT   540
CATTCGTACA TTCTTTGTCT CTGTTTCAGT AACATAGAAA GGTTTGTCTT GGGTGTTTTC   600
CTTCTTGAAT TGTTTCTCCC AAAGACCCTT GAAGTACAAT GCATTGACAA GAACCATTCT   660
TGAATCCTGG TCTAGATCAC CGGCTTTGAT CAAATCATGA ATTTTGTCAT GAGTTTTTTC   720
TTCAACCCAA GTGTTGATAA CTTTAGCGCT TTCAGCATTT TGGGCAAAGT TCAAGTTTTC   780
TGCTCCAGCT AAGAATTTGT TGGTGGCAAC TTCTTTGAAG GTGGGTTTTA ATGTATAGCC   840
TTCCATAACA TAAACTTTAT TGGCAATTTC CAGAGTTACA CCTTTTTGTG TATTAAGAGT   900
GTTCATCAAT GCGTGGTAGT CATCTTGAAT TTTTTCTTTT GATTGAGGCT GACGTAAACC   960
AGCAGCTATT TGTGTGGCAG TATTACCACC AGCTCCCATT GACACCAGGG ATAGAACAGT  1020
```

```
TTGTACAGAC AATGGGGACA TGATGAGATT GTCTTTGTTG CCAGAAGCAA CCGTATTGTA  1080
CAGGCTTCCA GCAAACTGGT TAATACTTGT AGACAATTCC TGGGGATCCG CCATTGTTGA  1140
AATTGGTATT AACACTGATA CAAAAAGAAA CACAAGTCGT GCGTGTTGAA CTAT        1194
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 376 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu
 1               5                  10                  15

Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
            20                  25                  30

Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly
        35                  40                  45

Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys
    50                  55                  60

Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr
65                  70                  75                  80

Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu
                85                  90                  95

Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe
            100                 105                 110

Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala
        115                 120                 125

Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His
    130                 135                 140

Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu
145                 150                 155                 160

Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys
                165                 170                 175

Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys
            180                 185                 190

Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe
        195                 200                 205

Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp
    210                 215                 220

Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Thr
225                 230                 235                 240

Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg
                245                 250                 255
```

```
Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu
            260                 265                 270

Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp
        275                 280                 285

Met Phe Met Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser
    290                 295                 300

Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu
305                 310                 315                 320

Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Val Met Leu
                325                 330                 335

Met Met Arg Cys Met Pro Met Met Pro Met Ala Phe Asn Ala Glu His
            340                 345                 350

Pro Phe Leu Tyr Phe Leu His Ser Lys Asn Ser Val Leu Phe Asn Gly
        355                 360                 365

Arg Leu Val Lys Pro Thr Thr Glu
    370                 375
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1454 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 20..1210

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
GAGCCGAAAT TTTAGCAAA ATG ATT AAC GCA CGA CTT GTG TTT CTT TTT GTA      52
                     Met Ile Asn Ala Arg Leu Val Phe Leu Phe Val
                       1               5                  10

TCA GTG TTA ATA CCA ATT TCA ACA ATG GCG GAT CCC CAG GAA TTG TCT      100
Ser Val Leu Ile Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser
            15                  20                  25

ACA AGT ATT AAC CAG TTT GCT GGA AGC CTG TAC AAT ACG GTT GCT TCT      148
Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser
        30                  35                  40

GGC AAC AAA GAC AAT CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT      196
Gly Asn Lys Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val
    45                  50                  55

CTA TCC CTG GTG TCA ATG GGA GCT GGT GGT AAT ACT GCC ACA CAA ATA      244
Leu Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile
 60                  65                  70                  75
```

```
GCT GCT GGT TTA CGT CAG CCT CAA TCA AAA GAA AAA ATT CAA GAT GAC      292
Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp
                 80                  85                  90

TAC CAT GCA TTG ATG AAC ACT CTT AAT ACA CAA AAA GGT GTA ACT CTG      340
Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu
             95                 100                 105

GAA ATT GCC AAC AAA GTT TAC GTT ATG GAA GGC TAT ACA TTG AAA CCC      388
Glu Ile Ala Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro
        110                 115                 120

ACC TTC AAA GAA GTT GCC ACC AAC AAA TTC TTA GCT GGA GCA GAA AAC      436
Thr Phe Lys Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn
    125                 130                 135

TTG AAC TTT GCC CAA AAT GCT GAA AGC GCT AAA GTT ATC AAC ACT TGG      484
Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp
140                 145                 150                 155

GTT GAA GAA AAA ACT CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT      532
Val Glu Glu Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly
                160                 165                 170

GAT CTA GAC CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC TTC      580
Asp Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe
            175                 180                 185

AAG GGT CTT TGG GAG AAA CAA TTC AAG AAG GAA AAC ACT CAA GAC AAA      628
Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys
        190                 195                 200

CCT TTC TAT GTT ACT GAA ACA GAG ACA AAG AAT GTA CGA ATG ATG CAC      676
Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn Val Arg Met Met His
    205                 210                 215

ATT AAG GAT AAA TTC CGT TAT GGA GAA TTT GAA GAA TTA GAT GCC AAG      724
Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys
220                 225                 230                 235

GCT GTA GAA TTG CCC TAC AGG AAC TCA GAT TTG GCC ATG TTA ATC ATT      772
Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile
                240                 245                 250

TTG CCA AAC AGC AAA ACT GGT CTC CCC GCT CTT GAA GAA AAA TTA CAA      820
Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln
            255                 260                 265

AAT GTT GAC TTG CAA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT      868
Asn Val Asp Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val
        270                 275                 280

ATT TTG GAT CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT      916
Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn
    285                 290                 295

GAT CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA      964
Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys
300                 305                 310                 315
```

```
GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT     1012
Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile
                320                 325                 330

TCT AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT GCT     1060
Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala
            335                 340                 345

GAA GCT GCA GCT GCC ACA GCT ACC TTT ATG GTT ACC TAT GAA CTG GAG     1108
Glu Ala Ala Ala Ala Thr Ala Thr Phe Met Val Thr Tyr Glu Leu Glu
        350                 355                 360

GTT TCC CTG GAT GAT CCA ACC GTT TTT AAA GTC GAT CAT CCA TTC AAT     1156
Val Ser Leu Asp Asp Pro Thr Val Phe Lys Val Asp His Pro Phe Asn
    365                 370                 375

ATT GTT TTG AAG ACA GGT GAT ACT GTA ATT TTT AAT GGG CGA GTT CAA     1204
Ile Val Leu Lys Thr Gly Asp Thr Val Ile Phe Asn Gly Arg Val Gln
380                 385                 390                 395

ACT CTA TGA AATGGATAGT GTAAGAAAAG AATACAAGAT CTATCTGAAT CTCTGGATTA 1263
Thr Leu

ATGAAGTAAT TTTTCTACAA TATTTTTTAA TAGTTATTAG GTCTAAAATA AGTTCATTTT   1323
TTAGTATGTG GTATAAATCG TGTAGACGAA AAATGTTTTG TTTTAGTTTT CACTTTTTAT   1383
GAATGTAATC ACCTATATAA TGTTGTAGTT TATGTAATAA AAATGTTAAA TGTGAAAAAA   1443
AAAAAAAAAA A                                                        1454
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 397 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Met Ile Asn Ala Arg Leu Val Phe Leu Phe Val Ser Val Leu Ile Pro
 1               5                  10                  15

Ile Ser Thr Met Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln
            20                  25                  30

Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn
        35                  40                  45

Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser
    50                  55                  60

Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg
65                  70                  75                  80

Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met
                85                  90                  95

Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys
            100                 105                 110

Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val
        115                 120                 125
```

Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln
    130   135   140

Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr
145   150   155   160

His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp
                165   170   175

Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu
            180   185   190

Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr
        195   200   205

Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp Lys Phe
    210   215   220

Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro
225   230   235   240

Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys
                245   250   255

Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln
            260   265   270

Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro
        275   280   285

Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
    290   295   300

Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly
305   310   315   320

Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln
                325   330   335

Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala
            340   345   350

Thr Ala Thr Phe Met Val Thr Tyr Glu Leu Glu Val Ser Leu Asp Asp
        355   360   365

Pro Thr Val Phe Lys Val Asp His Pro Phe Asn Ile Val Leu Lys Thr
    370   375   380

Gly Asp Thr Val Ile Phe Asn Gly Arg Val Gln Thr Leu
385   390   395

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1454 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
TTTTTTTTTT TTTTTTTCAC ATTTAACATT TTTATTACAT AAACTACAAC ATTATATAGG   60
TGATTACATT CATAAAAAGT GAAAACTAAA ACAAAACATT TTTCGTCTAC ACGATTTATA  120
CCACATACTA AAAAATGAAC TTATTTTAGA CCTAATAACT ATTAAAAAAT ATTGTAGAAA  180
AATTACTTCA TTAATCCAGA GATTCAGATA GATCTTGTAT TCTTTTCTTA CACTATCCAT  240
TTCATAGAGT TTGAACTCGC CCATTAAAAA TTACAGTATC ACCTGTCTTC AAAACAATAT  300
TGAATGGATG ATCGACTTTA AAAACGGTTG GATCATCCAG GGAAACCTCC AGTTCATAGG  360
TAACCATAAA GGTAGCTGTG GCAGCTGCAG CTTCAGCACC TTCTTCATTT ACTTCAATGA  420
AAGCTTTTTG AATTACTTTA GAAATATATA ACATCTCATC AGATCCTTCA AGCAATCCTT  480
TGAAATCAGC TTTTCCAGGA ACAAACATAT CAGACATACC CAACTTTTTC AGAGGATCAT  540
TCAAATTAAT TTCAGATTCA ATCTTGAATT TAGGCAGATC CAAAATAACT TCAACAGAGT  600
ACATGCGTTG AGTCAAGTTT TGCAAGTCAA CATTTTGTAA TTTTTCTTCA AGAGCGGGGA  660
GACCAGTTTT GCTGTTTGGC AAAATGATTA ACATGGCCAA ATCTGAGTTC CTGTAGGGCA  720
ATTCTACAGC CTTGGCATCT AATTCTTCAA ATTCTCCATA ACGGAATTTA TCCTTAATGT  780
GCATCATTCG TACATTCTTT GTCTCTGTTT CAGTAACATA GAAAGGTTTG TCTTGAGTGT  840
TTTCCTTCTT GAATTGTTTC TCCCAAAGAC CCTTGAAGTA CAATGCATTG ACAAGAACCA  900
TTCTTGAATC CTGGTCTAGA TCACCGGCTT TGATCAAATC ATGAATTTTG TCATGAGTTT  960
TTTCTTCAAC CCAAGTGTTG ATAACTTTAG CGCTTTCAGC ATTTTGGGCA AAGTTCAAGT 1020
TTTCTGCTCC AGCTAAGAAT TTGTTGGTGG CAACTTCTTT GAAGGTGGGT TTCAATGTAT 1080
AGCCTTCCAT AACGTAAACT TTGTTGGCAA TTTCCAGAGT TACACCTTTT TGTGTATTAA 1140
GAGTGTTCAT CAATGCATGG TAGTCATCTT GAATTTTTTC TTTTGATTGA GGCTGACGTA 1200
AACCAGCAGC TATTTGTGTG GCAGTATTAC CACCAGCTCC CATTGACACC AGGGATAGAA 1260
CAGTTTGTAC AGACAATGGG GACATGATGA GATTGTCTTT GTTGCCAGAA GCAACCGTAT 1320
TGTACAGGCT TCCAGCAAAC TGGTTAATAC TTGTAGACAA TTCCTGGGGA TCCGCCATTG 1380
TTGAAATTGG TATTAACACT GATACAAAAA GAAACACAAG TCGTGCGTTA ATCATTTTGC 1440
TAAAATTTCG GCTC                                                   1454
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1191 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
ATGATTAACG CACGACTTGT GTTTCTTTTT GTATCAGTGT TAATACCAAT TTCAACAATG   60
GCGGATCCCC AGGAATTGTC TACAAGTATT AACCAGTTTG CTGGAAGCCT GTACAATACG  120
GTTGCTTCTG GCAACAAAGA CAATCTCATC ATGTCCCCAT TGTCTGTACA AACTGTTCTA  180
TCCCTGGTGT CAATGGGAGC TGGTGGTAAT ACTGCCACAC AAATAGCTGC TGGTTTACGT  240
CAGCCTCAAT CAAAAGAAAA AATTCAAGAT GACTACCATG CATTGATGAA CACTCTTAAT  300
ACACAAAAAG GTGTAACTCT GGAAATTGCC AACAAAGTTT ACGTTATGGA AGGCTATACA  360
TTGAAACCCA CCTTCAAAGA AGTTGCCACC AACAAATTCT TAGCTGGAGC AGAAAACTTG  420
AACTTTGCCC AAAATGCTGA AAGCGCTAAA GTTATCAACA CTTGGGTTGA AGAAAAAACT  480
CATGACAAAA TTCATGATTT GATCAAAGCC GGTGATCTAG ACCAGGATTC AAGAATGGTT  540
CTTGTCAATG CATTGTACTT CAAGGGTCTT TGGGAGAAAC AATTCAAGAA GGAAAACACT  600
CAAGACAAAC CTTTCTATGT TACTGAAACA GAGACAAAGA ATGTACGAAT GATGCACATT  660
AAGGATAAAT TCCGTTATGG AGAATTTGAA GAATTAGATG CCAAGGCTGT AGAATTGCCC  720
TACAGGAACT CAGATTTGGC CATGTTAATC ATTTTGCCAA ACAGCAAAAC TGGTCTCCCC  780
GCTCTTGAAG AAAAATTACA AAATGTTGAC TTGCAAAACT TGACTCAACG CATGTACTCT  840
GTTGAAGTTA TTTTGGATCT GCCTAAATTC AAGATTGAAT CTGAAATTAA TTTGAATGAT  900
CCTCTGAAAA AGTTGGGTAT GTCTGATATG TTTGTTCCTG GAAAAGCTGA TTTCAAAGGA  960
TTGCTTGAAG GATCTGATGA GATGTTATAT ATTTCTAAAG TAATTCAAAA AGCTTTCATT 1020
GAAGTAAATG AAGAAGGTGC TGAAGCTGCA GCTGCCACAG CTACCTTTAT GGTTACCTAT 1080
GAACTGGAGG TTTCCCTGGA TGATCCAACC GTTTTTAAAG TCGATCATCC ATTCAATATT 1140
GTTTTGAAGA CAGGTGATAC TGTAATTTTT AATGGGCGAG TTCAAACTCT A          1191
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1191 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
TAGAGTTTGA ACTCGCCCAT TAAAAATTAC AGTATCACCT GTCTTCAAAA CAATATTGAA    60
TGGATGATCG ACTTTAAAAA CGGTTGGATC ATCCAGGGAA ACCTCCAGTT CATAGGTAAC   120
CATAAAGGTA GCTGTGGCAG CTGCAGCTTC AGCACCTTCT TCATTTACTT CAATGAAAGC   180
TTTTTGAATT ACTTTAGAAA TATATAACAT CTCATCAGAT CCTTCAAGCA ATCCTTTGAA   240
ATCAGCTTTT CCAGGAACAA ACATATCAGA CATACCCAAC TTTTTCAGAG GATCATTCAA   300
ATTAATTTCA GATTCAATCT TGAATTTAGG CAGATCCAAA ATAACTTCAA CAGAGTACAT   360
GCGTTGAGTC AAGTTTTGCA AGTCAACATT TTGTAATTTT TCTTCAAGAG CGGGGAGACC   420
AGTTTTGCTG TTTGGCAAAA TGATTAACAT GGCCAAATCT GAGTTCCTGT AGGGCAATTC   480
TACAGCCTTG GCATCTAATT CTTCAAATTC TCCATAACGG AATTTATCCT TAATGTGCAT   540
CATTCGTACA TTCTTTGTCT CTGTTTCAGT AACATAGAAA GGTTTGTCTT GAGTGTTTTC   600
CTTCTTGAAT TGTTTCTCCC AAAGACCCTT GAAGTACAAT GCATTGACAA GAACCATTCT   660
TGAATCCTGG TCTAGATCAC CGGCTTTGAT CAAATCATGA ATTTTGTCAT GAGTTTTTTC   720
TTCAACCCAA GTGTTGATAA CTTTAGCGCT TTCAGCATTT TGGGCAAAGT TCAAGTTTTC   780
TGCTCCAGCT AAGAATTTGT TGGTGGCAAC TTCTTTGAAG GTGGGTTTCA ATGTATAGCC   840
TTCCATAACG TAAACTTTGT TGGCAATTTC CAGAGTTACA CCTTTTTGTG TATTAAGAGT   900
GTTCATCAAT GCATGGTAGT CATCTTGAAT TTTTTCTTTT GATTGAGGCT GACGTAAACC   960
AGCAGCTATT TGTGTGGCAG TATTACCACC AGCTCCCATT GACACCAGGG ATAGAACAGT  1020
TTGTACAGAC AATGGGGACA TGATGAGATT GTCTTTGTTG CCAGAAGCAA CCGTATTGTA  1080
CAGGCTTCCA GCAAACTGGT TAATACTTGT AGACAATTCC TGGGGATCCG CCATTGTTGA  1140
AATTGGTATT AACACTGATA CAAAAAGAAA CACAAGTCGT GCGTTAATCA T           1191
```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 376 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu
  1               5                  10                  15

Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
             20                  25                  30

Leu Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly Gly
         35                  40                  45

Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys
     50                  55                  60

Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr
 65                  70                  75                  80

Gln Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu
                 85                  90                  95
```

Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys Phe
100 105 110

Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala
115 120 125

Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His
130 135 140

Asp Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val Leu
145 150 155 160

Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys
165 170 175

Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys
180 185 190

Asn Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe
195 200 205

Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser Asp
210 215 220

Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala
225 230 235 240

Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg
245 250 255

Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile Glu
260 265 270

Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp
275 280 285

Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser
290 295 300

Asp Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu
305 310 315 320

Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Thr Phe Met
325 330 335

Val Thr Tyr Glu Leu Glu Val Ser Leu Asp Asp Pro Thr Val Phe Lys
340 345 350

Val Asp His Pro Phe Asn Ile Val Leu Lys Thr Gly Asp Thr Val Ile
355 360 365

Phe Asn Gly Arg Val Gln Thr Leu
370 375

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GTGTTTCTTT TTGTATCAGT G 21

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CGGAATTCTT TAAAGGGATT TAACAC 26

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CGGAATTCTA ATTGGTAAAT CTC 23

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CGGAATTCTT TTATTCAGTT GTTGG 25

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CGGAATTCAT AGAGTTTGAA CTC 23

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CAAAACTGGT CTCCCCGCTC 20

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

ATTACAAAAT GTTGACTTGC 20

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TAATACGACT CACTATAGGG 20

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..404

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```
TT GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA    44
   Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
    1               5                  10
```

```
CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC       86
Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG      128
Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                 35                  40

TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC      170
Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
         45                  50                 55

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT      212
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
             60                  65                  70

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT      254
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                 75                  80

GCT GAA GCT GCA GCT GCC ACA GGA GGT TTC ATA ATG GCC GTA      296
Ala Glu Ala Ala Ala Ala Thr Gly Gly Phe Ile Met Ala Val
 85                  90                  95

TCC TTA CCT TTA CCA CCT GAG ACT TTT AAT GCT GAC CAT CCC      338
Ser Leu Pro Leu Pro Pro Glu Thr Phe Asn Ala Asp His Pro
    100                 105                 110

TTC TAT TTT GTG ATC TTC GAC AAA TCT TCC AAA GTG ACA ATG      380
Phe Tyr Phe Val Ile Phe Asp Lys Ser Ser Lys Val Thr Met
        115                 120                 125

TTC CAT GGT CAA CAC GTT AAT CCT TAA GAGTAACAAG GCAAATTTTG    427
Phe His Gly Gln His Val Asn Pro
            130

ATAATTAATT GTGATAAATT GCACGTTGTA AAAATGCTTC TTGATGCATA       477
TTTGATAATA TAATGTAAAG CCAAAAAAAA AAAAAAAAAA AAAAACTCGA       527
GGGGGGCCCG GTACCCAATT CG                                     549
```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 134 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```
Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
  1               5                  10

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                 35                  40

Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
         45                  50                 55
```

```
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
            60                  65                  70

Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                75                  80

Ala Glu Ala Ala Ala Ala Thr Gly Gly Phe Ile Met Ala Val
 85                  90                  95

Ser Leu Pro Leu Pro Pro Glu Thr Phe Asn Ala Asp His Pro
    100                 105                 110

Phe Tyr Phe Val Ile Phe Asp Lys Ser Ser Lys Val Thr Met
        115                 120                 125

Phe His Gly Gln His Val Asn Pro
            130
```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```
CGAATTGGGT ACCGGGCCCC CCTCGAGTTT TTTTTTTTTT TTTTTTTTTT         50
GGCTTTACAT TATATTATCA AATATGCATC AAGAAGCATT TTTACAACGT        100
GCAATTTATC ACAATTAATT ATCAAAATTT GCCTTGTTAC TCTTAAGGAT        150
TAACGTGTTG ACCATGGAAC ATTGTCACTT TGGAAGATTT GTCGAAGATC        200
ACAAAATAGA AGGGATGGTC AGCATTAAAA GTCTCAGGTG GTAAAGGTAA        250
GGATACGGCC ATTATGAAAC CTCCTGTGGC AGCTGCAGCT TCAGCACCTT        300
CTTCATTTAC TTCAATGAAA GCTTTTTGAA TTACTTTAGA AATATATAAC        350
ATCTCATCAG ATCCTTCAAG CAATCCTTTG AAATCAGCTT TTCCAGGAAC        400
AAACATATCA GACATACCCA ACTTTTTCAG AGGATCATTC AAATTAATTT        450
CAGATTCAAT CTTGAATTTA GGCAGATCCA AAATAACTTC AACAGAGTAC        500
ATGCGTTGAG TCAAGTTTTG CAAGTCAACA TTTTGTAATT TTTCTTCAA         549
```

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..449

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
TT GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA    44
   Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
     1               5                  10
```

```
CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC        88
Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG       128
Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                  35                  40

TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC       170
Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
         45                  50                  55

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT       212
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
             60                  65                  70

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT       254
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                 75                  80

GCT GAA GCT GCA GCT GCC ACA GGA GTG CTC ATA GAA TTG GAC       296
Ala Glu Ala Ala Ala Ala Thr Gly Val Leu Ile Glu Leu Asp
 85                 90                  95

TCT TTT ATG CCT GAT CGA GTA TTT GAA GCA AAT CAT CCC TTC       338
Ser Phe Met Pro Asp Arg Val Phe Glu Ala Asn His Pro Phe
    100                 105                 110

TAT TTC GCC CTC TAC ACA AAA TCT GCA CAA AAA CCA GAA CAA       380
Tyr Phe Ala Leu Tyr Thr Lys Ser Ala Gln Lys Pro Glu Gln
        115                 120                 125

TCC AAA AAG CGA GCG CGC TCT AAA ATT GTT ACA GTA CTG TTT       422
Ser Lys Lys Arg Ala Arg Ser Lys Ile Val Thr Val Leu Phe
            130                 135                 140

TCT GGA CGT TTA ACC AAT ATT AAT AAC TAGAATAATA TGGAATTCTA    469
Ser Gly Arg Leu Thr Asn Ile Asn Asn
                145

TTTTTGTGAA ATAAACAGGA TAAATAATGA AGTAAAAAAA AAAAAAAAAA        519
AACTCGAGGG GGGGCCCGGT ACCCAATTCG                              549
```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 149 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
  1               5                  10

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25
```

Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
30 35 40

Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
45 50 55

Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
60 65 70

Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
75 80

Ala Glu Ala Ala Ala Ala Thr Gly Val Leu Ile Glu Leu Asp
85 90 95

Ser Phe Met Pro Asp Arg Val Phe Glu Ala Asn His Pro Phe
100 105 110

Tyr Phe Ala Leu Tyr Thr Lys Ser Ala Gln Lys Pro Glu Gln
115 120 125

Ser Lys Lys Arg Ala Arg Ser Lys Ile Val Thr Val Leu Phe
130 135 140

Ser Gly Arg Leu Thr Asn Ile Asn Asn
145

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```
CGAATTGGGT ACCGGGCCCC CCCTCGAGTT TTTTTTTTTT TTTTTTTACT     50
TCATTATTTA TCCTGTTTAT TTCACAAAAA TAGAATTCCA TATTATTCTA    100
GTTATTAATA TTGGTTAAAC GTCCAGAAAA CAGTACTGTA ACAATTTTAG    150
AGCGCGCTCG CTTTTTGGAT TGTTCTGGTT TTTGTGCAGA TTTTGTGTAG    200
AGGGCGAAAT AGAAGGGATG ATTTGCTTCA AATACTCGAT CAGGCATAAA    250
AGAGTCCAAT TCTATGAGCA CTCCTGTGGC AGCTGCAGCT TCAGCACCTT    300
CTTCATTTAC TTCAATGAAA GCTTTTTGAA TTACTTTAGA AATATATAAC    350
ATCTCATCAG ATCCTTCAAG CAATCCTTTG AAATCAGCTT TTCCAGGAAC    400
AAACATATCA GACATACCCA ACTTTTTCAG AGGATCATTC AAATTAATTT    450
CAGATTCAAT CTTGAATTTA GGCAGATCCA AAATAACTTC AACAGAGTAC    500
ATGCGTTGAG TCAAGTTTTG CAAGTCAACA TTTTGTAATT TTTCTTCAA     549
```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 581 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..410

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
TT GAA GAA AAA TTA CAA AAT GTT GAT TTG CAA AAC TTG ACT CAA    44
   Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
     1               5                  10

CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC       86
Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                  20                  25

AAA ATT GAG TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG      128
Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                  35                  40

TTG GGT ATG TCT GAT ATG TTC ATG CCT GGA AAA GCT GAT TTC      170
Leu Gly Met Ser Asp Met Phe Met Pro Gly Lys Ala Asp Phe
         45                  50                  55

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT      212
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
             60                  65                  70

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT      254
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                 75                  80

GCT GAA GCT GCA GCT GCC ACA GCT GTC TTA GCA GTG GCT TTT      296
Ala Glu Ala Ala Ala Ala Thr Ala Val Leu Ala Val Ala Phe
 85                  90                  95

TCA CTG AGT TTT CCT GCA GAT CCT GTG CTT TTC ACG GCT GAT      338
Ser Leu Ser Phe Pro Ala Asp Pro Val Leu Phe Thr Ala Asp
    100                 105                 110

CAT CCT TTC CAT TAT TTG CTA ATA GAT CGA TCT CAA CAT AAT      380
His Pro Phe His Tyr Leu Leu Ile Asp Arg Ser Gln His Asn
        115                 120                 125

CTA CCT CTT TTT AAA GGA CGA TTT GTG CAA TAA TCCATTTGGA       423
Leu Pro Leu Phe Lys Gly Arg Phe Val Gln
            130                 135

TTTAACATAT TATTGATCAC TTGTGTGTTT TAATTTAATG CATTTTTATT       473
TGTTAATGTT GCCCCAAATA TTAGCAATTT GTATTTAAAT AAATTTATTT       523
CGTGCTTGTT ATAAAAAAAA AAAAAAAAAA CTCGAGGGGG GGCCCGGTAC       573
CCAATTCG                                                     581
```

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 136 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
 1               5                  10

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                 35                  40

Leu Gly Met Ser Asp Met Phe Met Pro Gly Lys Ala Asp Phe
         45                 50                  55

Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
             60                 65                  70

Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                 75                 80

Ala Glu Ala Ala Ala Ala Thr Ala Val Leu Ala Val Ala Phe
 85                 90                  95

Ser Leu Ser Phe Pro Ala Asp Pro Val Leu Phe Thr Ala Asp
    100                105                 110

His Pro Phe His Tyr Leu Leu Ile Asp Arg Ser Gln His Asn
        115                120                 125

Leu Pro Leu Phe Lys Gly Arg Phe Val Gln
            130                135
```

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 581 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
CGAATTGGGT ACCGGGCCCC CCCTCGAGTT TTTTTTTTTT TTTTTTATAA    50
CAAGCACGAA ATAAATTTAT TTAAATACAA ATTGCTAATA TTTGGGGCAA   100
CATTAACAAA TAAAAATGCA TTAAATTAAA ACACACAAGT GATCAATAAT   150
ATGTTAAATC CAAATGGATT ATTGCACAAA TCGTCCTTTA AAAAGAGGTA   200
GATTATGTTG AGATCGATCT ATTAGCAAAT AATGGAAAGG ATGATCAGCC   250
GTGAAAAGCA CAGGATCTGC AGGAAAACTC AGTGAAAAAG CCACTGCTAA   300
GACAGCTGTG GCAGCTGCAG CTTCAGCACC TTCTTCATTT ACTTCAATGA   350
AAGCTTTTTG AATTACTTTA GAAATATATA ACATCTCATC AGATCCTTCA   400
AGCAATCCTT TGAAATCAGC TTTTCCAGGC ATGAACATAT CAGACATACC   450
CAACTTTTTC AGAGGATCAT TCAAATTAAT TTCAGACTCA ATTTTGAATT   500
TAGGCAGATC CAAAATAACT TCAACAGAGT ACATGCGTTG AGTCAAGTTT   550
TGCAAATCAA CATTTTGTAA TTTTTCTTCA A                       581
```

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 654 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..356

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

```
AA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT      44
   Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
    1               5                  10

CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT         86
Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
 15                  20                  25

CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA        128
Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly
     30                  35                  40

AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG        170
Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
         45                  50                  55

TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA        212
Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
             60                  65                  70

AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GAG TAC TGC        254
Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Glu Tyr Cys
                 75                  80

TCC CTG AAC TGG TCT CGT ATA TTG TAC GTC CTC CTC CAA AGG        296
Ser Leu Asn Trp Ser Arg Ile Leu Tyr Val Leu Leu Gln Arg
 85                  90                  95

TTT TCA AAG TTG ATC ACC CCT TTC CCA TTT TAT CAT AAG GAC        338
Phe Ser Lys Leu Ile Thr Pro Phe Pro Phe Tyr His Lys Asp
    100                 105                 110

TTC GAA CAC ACT TTT GTT TGA TGGGCGCGTC AGAACGCCAT              379
Phe Glu His Thr Phe Val
        115

GAAAAGCTAA TTTTCTTAAA CGAAGGATTC CAAGATCTAT CTGAATCTCT         429
GGATTAATGA AGTAATTTTT CTACAATATT TTTTAATAGT TATTAGGTCT         479
AAAATAAGTT CATTTTTTAG TATGTGGTAT AAATCGTGTA GACGAAAAAT         529
GTTTTGTTTT AGTTTTCACT TTTTATGAAT GTAATCACCT ATATAATGTT         579
GTAGTTTATG TAATAAAAAT GTTAAATGTA AAAAAAAAAA AAAAAAACTC         629
GAGGGGGGGC CCGGTACCCA ATTCG                                    654
```

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 118 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

```
Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
 1               5                  10

Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
 15                 20                  25

Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly
     30                 35                  40

Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
         45                 50                  55

Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
             60                 65                  70

Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Glu Tyr Cys
                 75                 80

Ser Leu Asn Trp Ser Arg Ile Leu Tyr Val Leu Leu Gln Arg
 85                 90                  95

Phe Ser Lys Leu Ile Thr Pro Phe Pro Phe Tyr His Lys Asp
    100                105                 110

Phe Glu His Thr Phe Val
        115
```

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 654 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

```
CGAATTGGGT ACCGGGCCCC CCCTCGAGTT TTTTTTTTTT TTTTTTACAT    50
TTAACATTTT TATTACATAA ACTACAACAT TATATAGGTG ATTACATTCA   100
TAAAAAGTGA AAACTAAAAC AAAACATTTT TCGTCTACAC GATTTATACC   150
ACATACTAAA AAATGAACTT ATTTTAGACC TAATAACTAT TAAAAAATAT   200
TGTAGAAAAA TTACTTCATT AATCCAGAGA TTCAGATAGA TCTTGGAATC   250
CTTCGTTTAA GAAAATTAGC TTTTCATGGC GTTCTGACGC GCCCATCAAA   300
CAAAAGTGTG TTCGAAGTCC TTATGATAAA ATGGGAAAGG GGTGATCAAC   350
TTTGAAAACC TTTGGAGGAG GACGTACAAT ATACGAGACC AGTTCAGGGA   400
GCAGTACTCT GTGGCAGCTG CAGCTTCAGC ACCTTCTTCA TTTACTTCAA   450
TGAAAGCTTT TTGAATTACT TTAGAAATAT ATAACATCTC ATCAGATCCT   500
TCAAGCAATC CTTTGAAATC AGCTTTTCCA GGAACAAACA TATCAGACAT   550
ACCCAACTTT TTCAGAGGAT CATTCAAATT AATTTCAGAT TCAATCTTGA   600
```

```
ATTTAGGCAG ATCCAAAATA ACTTCAACAG AGTACATGCG TTGAGTCAAG        650
TTTT                                                          654
```

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 670 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..377

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```
AA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT    44
   Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
     1               5                  10

CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT       86
Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
 15                  20                  25

CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTC ATG CCT GGA      128
Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Met Pro Gly
     30                  35                  40

AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG      170
Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
         45                  50                  55

TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA      212
Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
             60                  65                  70

AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GGT GTA ATT      254
Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Val Ile
                 75                  80

ATG GTT GCA TTT ATG TCG TAT ATC GTA CCA CCT CCT CCA ACC      296
Met Val Ala Phe Met Ser Tyr Ile Val Pro Pro Pro Pro Thr
 85                  90                  95

ATT TTT AAA GTT GAT CAT CCT TTC CAC TTT GTC TTA AAG ACT      338
Ile Phe Lys Val Asp His Pro Phe His Phe Val Leu Lys Thr
    100                 105                 110

TCG GAT ACT GTT TTG TTT GAT GGG AGG GTT CGA CTT CCA TAA      380
Ser Asp Thr Val Leu Phe Asp Gly Arg Val Arg Leu Pro
        115                 120                 125

ATGATAATGA TGTGATTTTC TTAAATAAAA GAATACAAGA TCTATCTGAA       430
TCTCCAGATT AATGAAGTAA TTTTTCTACA ATATTTTTTA ATAGTTATTA       480
GGTCTAAAAT AAGTTCATTT TTTAGTATGT GGTATAAATC GTGTAGACGA       530
AAAATGTTTT GTTTTAGTTT TCACTTTTTA TGAATGTAAT CACCTATATA       580
ATGTTGTAGT TTATGTAATA AAAATGTTAA ATGTGAAAAA AAAAAAAAAA       630
AAAAAAAAAA AACTCGAGGG GGGGCCCGGT ACCCAATTCG                  670
```

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 125 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

```
Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
 1               5                  10

Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
 15                  20                  25

Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Met Pro Gly
    30                  35                  40

Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
        45                  50                  55

Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
            60                  65                  70

Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Val Ile
                75                  80

Met Val Ala Phe Met Ser Tyr Ile Val Pro Pro Pro Pro Thr
 85                  90                  95

Ile Phe Lys Val Asp His Pro Phe His Phe Val Leu Lys Thr
    100                 105                 110

Ser Asp Thr Val Leu Phe Asp Gly Arg Val Arg Leu Pro
        115                 120                 125
```

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 670 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

```
CGAATTGGGT ACCGGGCCCC CCCTCGAGTT TTTTTTTTTT TTTTTTTTTT    50
TTTTTCACAT TTAACATTTT TATTACATAA ACTACAACAT TATATAGGTG   100
ATTACATTCA TAAAAAGTGA AAACTAAAAC AAAACATTTT TCGTCTACAC   150
GATTTATACC ACATACTAAA AAATGAACTT ATTTTAGACC TAATAACTAT   200
TAAAAAATAT TGTAGAAAAA TTACTTCATT AATCTGGAGA TTCAGATAGA   250
TCTTGTATTC TTTTATTTAA GAAAATCACA TCATTATCAT TTATGGAAGT   300
CGAACCCTCC CATCAAACAA AACAGTATCC GAAGTCTTTA AGACAAAGTG   350
GAAAGGATGA TCAACTTTAA AAATGGTTGG AGGAGGTGGT ACGATATACG   400
ACATAAATGC AACCATAATT ACACCTGTGG CAGCTGCAGC TTCAGCACCT   450
TCTTCATTTA CTTCAATGAA AGCTTTTTGA ATTACTTTAG AAATATATAA   500
CATCTCATCA GATCCTTCAA GCAATCCTTT GAAATCAGCT TTTCCAGGCA   550
TGAACATATC AGACATACCC AACTTTTTCA GAGGATCATT CAAATTAATT   600
```

```
TCAGATTCAA TCTTGAATTT AGGCAGATCC AAAATAACTT CAACAGAGTA      650
CATGCGTTGA GTCAAGTTTT                                       670
```

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 706 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..410

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

```
TT GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA    44
   Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
    1               5                  10

CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC       86
Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG      128
Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                  35                  40

TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC      170
Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
         45                  50                  55

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT      212
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
             60                  65                  70

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT      254
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                 75                  80

GCT GAA GCT GCA GCT GCC ACA GGA ATC GTT AGT TTT GGC TCA      296
Ala Glu Ala Ala Ala Ala Thr Gly Ile Val Ser Phe Gly Ser
 85                 90                  95

TCT CTG TAT GTC GAC AAT CGT CCT CCA GTT GCT TTT ACC GTA      338
Ser Leu Tyr Val Asp Asn Arg Pro Pro Val Ala Phe Thr Val
    100                 105                 110

GAT CAC CCA TTC TAC TAT ACT TTA AAT ACT TGG GAT ACT CTT      380
Asp His Pro Phe Tyr Tyr Thr Leu Asn Thr Trp Asp Thr Leu
        115                 120                 125

TTG TTC AAT GGG CGA GTT ATA TCT CCC AAA TAA AAGGCGTTTA       423
Leu Phe Asn Gly Arg Val Ile Ser Pro Lys
            130                 135

TTGAGAAGAA TACAAGATCT ATCTGAATCT CTGGATTAAT GAAGTAATTT       473
TTCTACAATA TTTTTTAATA GTTATTAGGT CTAAAATAAG TTCATTTTTT       523
AGTATGTGGT ATAAATCGTG TAGACGAAAA ATGTTTTGTT TTAGTTTTCA       573
```

CTTTTTATGA ATGTAATCAC CTATATAATG TTGTAGTTTA TGTAATAAAA 623
ATGTTAAATG TGAAAATATA TTTGATACTA ATAATTAAAA AAAAAAAAAA 673
AAAACTCGAG GGGGGGCCCG GTACCCAATT TCG 706

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 136 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
1 5 10

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
15 20 25

Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
30 35 40

Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
45 50 55

Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
60 65 70

Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
75 80

Ala Glu Ala Ala Ala Ala Thr Gly Ile Val Ser Phe Gly Ser
85 90 95

Ser Leu Tyr Val Asp Asn Arg Pro Pro Val Ala Phe Thr Val
100 105 110

Asp His Pro Phe Tyr Tyr Thr Leu Asn Thr Trp Asp Thr Leu
115 120 125

Leu Phe Asn Gly Arg Val Ile Ser Pro Lys
130 135

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 706 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CGAAATTGGG TACCGGGCCC CCCCTCGAGT TTTTTTTTTT TTTTTTTAAT 50
TATTAGTATC AAATATATTT TCACATTTAA CATTTTTATT ACATAAACTA 100
CAACATTATA TAGGTGATTA CATTCATAAA AAGTGAAAAC TAAAACAAAA 150
CATTTTTCGT CTACACGATT TATACCACAT ACTAAAAAAT GAACTTATTT 200
TAGACCTAAT AACTATTAAA AAATATTGTA GAAAAATTAC TTCATTAATC 250

```
CAGAGATTCA GATAGATCTT GTATTCTTCT CAATAAACGC CTTTTATTTG       300
GGAGATATAA CTCGCCCATT GAACAAAAGA GTATCCCAAG TATTTAAAGT       350
ATAGTAGAAT GGGTGATCTA CGGTAAAAGC AACTGGAGGA CGATTGTCGA       400
CATACAGAGA TGAGCCAAAA CTAACGATTC CTGTGGCAGC TGCAGCTTCA       450
GCACCTTCTT CATTTACTTC AATGAAAGCT TTTTGAATTA CTTTAGAAAT       500
ATATAACATC TCATCAGATC CTTCAAGCAA TCCTTTGAAA TCAGCTTTTC       550
CAGGAACAAA CATATCAGAC ATACCCAACT TTTTCAGAGG ATCATTCAAA       600
TTAATTTCAG ATTCAATCTT GAATTTAGGC AGATCCAAAA TAACTTCAAC       650
AGAGTACATG CGTTGAGTCA AGTTTTGCAA GTCAACATTT TGTAATTTTT       700
CTTCAA                                                       706
```

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 623 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..368

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

```
AA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT    44
   Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
     1               5                  10

CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT      86
Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
 15                  20                  25

CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA     128
Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly
     30                  35                  40

AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG     170
Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
         45                  50                  55

TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA     212
Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
             60                  65                  70

AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GGA TTA TTT     254
Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Leu Phe
                 75                  80

TTC TCA ATA ACG TCC TTC CAA GAA CCG ACT TTA TTC GAA GCT     296
Phe Ser Ile Thr Ser Phe Gln Glu Pro Thr Leu Phe Glu Ala
 85                  90                  95

GAC CGA CCT TTT ATG TTC ATC TTA CGT ACT CAG GAA AAT CCT     338
Asp Arg Pro Phe Met Phe Ile Leu Arg Thr Gln Glu Asn Pro
    100                 105                 110

ATT CTA CTA TTT TCC GGT CAT TTT GTC GAA TGA TGAACTTAGA      381
Ile Leu Leu Phe Ser Gly His Phe Val Glu
        115                 120
```

```
ATACAAGATC TATCTGAATC TCTGGATTAA TGAAGTAATT TTTCTACAAT     431
ATTTTTTAAT AGTTATTAGG TCTAAAATAA GTTCATTTTT TAGTATGTGG     481
TATAAATCGT GTAGACGAAA AATGTTTTGT TTTAGTTTTC ACTTTTATGA     531
ATGTATCACC TATATAATGT GTAGTTATGT ATAAAATGTT AAATGTGAAA     581
AAAAAAAAAA AAAAAACTCG AGGGGGGGCC GGTACCAATT CG             623
```

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```
Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
 1               5                  10

Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
 15                 20                  25

Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly
     30                 35                  40

Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
         45                 50                  55

Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
             60                 65                  70

Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly Leu Phe
                 75                  80

Phe Ser Ile Thr Ser Phe Gln Glu Pro Thr Leu Phe Glu Ala
 85                 90                  95

Asp Arg Pro Phe Met Phe Ile Leu Arg Thr Gln Glu Asn Pro
    100                 105                 110

Ile Leu Leu Phe Ser Gly His Phe Val Glu
        115                 120
```

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 623 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

```
CGAATTGGTA CCGGCCCCCC CTCGAGTTTT TTTTTTTTTT TTTTTCACAT      50
TTAACATTTT ATACATAACT ACACATTATA TAGGTGATAC ATTCATAAAA     100
GTGAAAACTA AAACAAAACA TTTTTCGTCT ACACGATTTA TACCACATAC     150
TAAAAAATGA ACTTATTTTA GACCTAATAA CTATTAAAAA ATATTGTAGA     200
AAAATTACTT CATTAATCCA GAGATTCAGA TAGATCTTGT ATTCTAAGTT     250
CATCATTCGA CAAAATGACC GGAAAATAGT AGAATAGGAT TTTCCTGAGT     300
```

```
ACGTAAGATG AACATAAAAG GTCGGTCAGC TTCGAATAAA GTCGGTTCTT      350
GGAAGGACGT TATTGAGAAA AATAATCCTG TGGCAGCTGC AGCTTCAGCA      400
CCTTCTTCAT TTACTTCAAT GAAAGCTTTT TGAATTACTT TAGAAATATA      450
TAACATCTCA TCAGATCCTT CAAGCAATCC TTTGAAATCA GCTTTTCCAG      500
GAACAAACAT ATCAGACATA CCCAACTTTT TCAGAGGATC ATTCAAATTA      550
ATTTCAGATT CAATCTTGAA TTTAGGCAGA TCCAAAATAA CTTCAACAGA      600
GTACATGCGT TGAGTCAAGT TTT                                   623
```

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 731 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..413

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

```
TT GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA      44
   Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
    1               5                  10

CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC         86
Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG        128
Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
    30                  35                  40

TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC        170
Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
        45                  50                  55

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT        212
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
            60                  65                  70

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT        254
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                75                  80

GCT GAA GCT GCA GCT GCC ACA GCC GTG TTT GCG ACT CGT CGT        296
Ala Glu Ala Ala Ala Ala Thr Ala Val Phe Ala Thr Arg Arg
 85                 90                  95

GTG ATC AAG GTG CTG GCG AAA GAA ATT TTC AAT TGC GAC CAT        338
Val Ile Lys Val Leu Ala Lys Glu Ile Phe Asn Cys Asp His
    100                 105                 110

CCG TTC TAC TTC GCC TTG GTT CAT TCG CAA GAA GGT ACC TCG        380
Pro Phe Tyr Phe Ala Leu Val His Ser Gln Glu Gly Thr Ser
        115                 120                 125
```

```
GCG CCT CTT TTC ACC GGC GCT TTC CGG ACG CCT TGA             416
Ala Pro Leu Phe Thr Gly Ala Phe Arg Thr Pro
            130                 135

TAAATGACAG TTCCATTTTC CGCACAATAA GAAAAATCAC GGAAAAGAGA      466
GAAAGTGGAA AGTAATACAA GATCTATCTG AATCTCTGGA TTAATGAAGT      516
AATTTTTCTA CAATATTTTT TAATAGTTAT TAAGTCTAAA ATAAGTTCAA      566
TTTTTAAGTA TGTGGTATAA ATCGTGTAGA CGAAAAATGT TTTGTTTTAA      616
GTTTCACTTT TAAGAAATGT ATCACCTATA TAATGTTGTA GTTTATGTAA      666
TAAAAATGTT AAATGTGAAA AAAAAAAAAA AAAAAACTCG AGGGGGGGCC      716
CGGTACCCAA TTTCG                                            731
```

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 137 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

```
Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
 1               5                  10

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
15                  20                  25

Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
    30                  35                  40

Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
        45                  50                  55

Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
            60                  65                  70

Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                75                  80

Ala Glu Ala Ala Ala Ala Thr Ala Val Phe Ala Thr Arg Arg
85                  90                  95

Val Ile Lys Val Leu Ala Lys Glu Ile Phe Asn Cys Asp His
    100                 105                 110

Pro Phe Tyr Phe Ala Leu Val His Ser Gln Glu Gly Thr Ser
        115                 120                 125

Ala Pro Leu Phe Thr Gly Ala Phe Arg Thr Pro
            130                 135
```

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 731 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```
CGAAATTGGG TACCGGGCCC CCCCTCGAGT TTTTTTTTTT TTTTTTTTCA    50
CATTTAACAT TTTTATTACA TAAACTACAA CATTATATAG GTGATACATT   100
TCTTAAAAGT GAAACTTAAA ACAAAACATT TTTCGTCTAC ACGATTTATA   150
CCACATACTT AAAAATTGAA CTTATTTTAG ACTTAATAAC TATTAAAAAA   200
TATTGTAGAA AAATTACTTC ATTAATCCAG AGATTCAGAT AGATCTTGTA   250
TTACTTTCCA CTTTCTCTCT TTTCCGTGAT TTTTCTTATT GTGCGGAAAA   300
TGGAACTGTC ATTTATCAAG GCGTCCGGAA AGCGCCGGTG AAAAGAGGCG   350
CCGAGGTACC TTCTTGCGAA TGAACCAAGG CGAAGTAGAA CGGATGGTCG   400
CAATTGAAAA TTTCTTTCGC CAGCACCTTG ATCACACGAC GAGTCGCAAA   450
CACGGCTGTG GCAGCTGCAG CTTCAGCACC TTCTTCATTT ACTTCAATGA   500
AAGCTTTTTG AATTACTTTA GAAATATATA ACATCTCATC AGATCCTTCA   550
AGCAATCCTT TGAAATCAGC TTTTCCAGGA ACAAACATAT CAGACATACC   600
CAACTTTTTC AGAGGATCAT TCAAATTAAT TTCAGATTCA ATCTTGAATT   650
TAGGCAGATC CAAAATAACT TCAACAGAGT ACATGCGTTG AGTCAAGTTT   700
TGCAAGTCAA CATTTTGTAA TTTTTCTTCA A                       731
```

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 685 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..407

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
TT GAA GAA AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA    44
   Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
     1               5                  10

CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC      86
Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
 15                 20                  25

AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG     128
Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
     30                  35                  40

TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC     170
Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
         45                  50                  55

AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT     212
Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
             60                  65                  70

AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT     254
Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                 75                  80

GCT GAA GCT GCA GCT GCC ACA GCT GTC GTG ATG CTT GGA TAT     296
Ala Glu Ala Ala Ala Ala Thr Ala Val Val Met Leu Gly Tyr
 85                  90                  95
```

```
TCC CTA ATT ACG TCT CGG GTA GCT CCA ACT GTT TTT AAC GTC      338
Ser Leu Ile Thr Ser Arg Val Ala Pro Thr Val Phe Asn Val
    100                 105                 110

GAT CAT CCA TTC CAT GTT GTA TTA AAA TCA AAT GAT GTT GTT      380
Asp His Pro Phe His Val Val Leu Lys Ser Asn Asp Val Val
        115                 120                 125

TTA TTT AAT GGA CGC GTT CAG TCA CCA TGA AATGGATATT           420
Leu Phe Asn Gly Arg Val Gln Ser Pro
            130                 135

TTTGGTAAAA GAATACAAGA TCTATCTGAA TCTCTGGATT AATGAAGTAA       470
TTTTTCTACA ATATTTTTTA ATAGTTATTA GGTCTAAAAT AAGTTCATTT       520
TTTAGTATGT GGTATAAATC GTGTAGACGA AAAATGTTTT GTTTTAGTTT       570
TCACTTTTTA TGAATGTAAT CACCTATATA ATGTTGTAGT TTATGTAATA       620
AAAATGTTAA ATGTGAAAAA AAAAAAAAAA AAAAAAACTC GAGGGGGGGC       670
CCGGTACCCA ATTCG                                             685
```

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 135 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
Glu Glu Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln
 1               5                  10

Arg Met Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe
15                  20                  25

Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys
    30                  35                  40

Leu Gly Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe
        45                  50                  55

Lys Gly Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser
            60                  65                  70

Lys Val Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly
                75                  80

Ala Glu Ala Ala Ala Ala Thr Ala Val Val Met Leu Gly Tyr
85                  90                  95

Ser Leu Ile Thr Ser Arg Val Ala Pro Thr Val Phe Asn Val
    100                 105                 110

Asp His Pro Phe His Val Val Leu Lys Ser Asn Asp Val Val
        115                 120                 125

Leu Phe Asn Gly Arg Val Gln Ser Pro
            130                 135
```

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 685 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

```
CGAATTGGGT ACCGGGCCCC CCCTCGAGTT TTTTTTTTTT TTTTTTTTTT      50
CACATTTAAC ATTTTTATTA CATAAACTAC AACATTATAT AGGTGATTAC     100
ATTCATAAAA AGTGAAAACT AAAACAAAAC ATTTTTCGTC TACACGATTT     150
ATACCACATA CTAAAAAATG AACTTATTTT AGACCTAATA ACTATTAAAA     200
AATATTGTAG AAAAATTACT TCATTAATCC AGAGATTCAG ATAGATCTTG     250
TATTCTTTTA CCAAAAATAT CCATTTCATG GTGACTGAAC GCGTCCATTA     300
AATAAAACAA CATCATTTGA TTTTAATACA ACATGGAATG GATGATCGAC     350
GTTAAAAACA GTTGGAGCTA CCCGAGACGT AATTAGGGAA TATCCAAGCA     400
TCACGACAGC TGTGGCAGCT GCAGCTTCAG CACCTTCTTC ATTTACTTCA     450
ATGAAAGCTT TTTGAATTAC TTTAGAAATA TATAACATCT CATCAGATCC     500
TTCAAGCAAT CCTTTGAAAT CAGCTTTTCC AGGAACAAAC ATATCAGACA     550
TACCCAACTT TTTCAGAGGA TCATTCAAAT TAATTTCAGA TTCAATCTTG     600
AATTTAGGCA GATCCAAAAT AACTTCAACA GAGTACATGC GTTGAGTCAA     650
GTTTTGCAAG TCAACATTTT GTAATTTTTC TTCAA                     685
```

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1222 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3.1220

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
AC GCG ATA GTT CAA CAC GCA CGA CTT GTG TTT CTT TTT GTA TCA     44
   Ala Ile Val Gln His Ala Arg Leu Val Phe Leu Phe Val Ser
     1               5                  10

GTG TTA ATA CCA ATT TCA ACA ATG GCG GAT CCC CAG GAA TTG        86
Val Leu Ile Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu
 15                 20                  25

TCT ACA AGT ATT AAC CAG TTT GCT GGA AGC CTG TAC AAT ACG       128
Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr
     30                  35                  40

GTT GCT TCT GGC AAC AAA GAC AAT CTC ATC ATG TCC CCA TTG       170
Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro Leu
         45                  50                  55

TCT GTA CAA ACT GTT CTA TCC CTG GTG TCA ATG GGA GCT GGT       212
Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly
             60                  65                  70
```

GGT AAT ACT GCC ACA CAA ATA GCT GCT GGT TTA CGT CAG CCT 254
Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro
75 80

CAA TCA AAA GAA AAA ATT CAA GAT GAC TAC CAT GCA TTG ATG 296
Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met
85 90 95

AAC ACT CTT AAT ACA CAA AAA GGT GTA ACT CTG GAA ATT GCC 338
Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala
100 105 110

AAC AAA GTT TAC GTT ATG GAA GGC TAT ACA TTG AAA CCC ACC 380
Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr
115 120 125

TTC AAA GAA GTT GCC ACC AAC AAA TTC TTA GCT GGA GCA GAA 422
Phe Lys Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu
130 135 140

AAC TTG AAC TTT GCC CAA AAT GCT GAA AGC GCT AAA GTT ATC 464
Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala Lys Val Ile
145 150

AAC ACT TGG GTT GAA GAA AAA ACT CAT GAC AAA ATT CAT GAT 506
Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His Asp
155 160 165

TTG ATC AAA GCC GGT GAT CTA GAC CAG GAT TCA AGA ATG GTT 548
Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val
170 175 180

CTT GTC AAT GCA TTG TAC TTC AAG GGT CTT TGG GAG AAA CAA 590
Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln
185 190 195

TTC AAG AAG GAA AAC ACT CAA GAC AAA CCT TTC TAT GTT ACT 632
Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr
200 205 210

GAA ACA GAG ACA AAG AAT GTA CGA ATG ATG CAC ATT AAG GAT 674
Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp
215 220

AAA TTC CGT TAT GGA GAA TTT GAA GAA TTA GAT GCC AAG GCT 716
Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala
225 230 235

GTA GAA TTG CCC TAC AGG AAC TCA GAT TTG GCC ATG TTA ATC 758
Val Glu Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile
240 245 250

ATT TTG CCA AAC AGC AAA ACT GGT CTC CCC GCT CTT GAA GAA 800
Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala Leu Glu Glu
255 260 265

AAA TTA CAA AAT GTT GAC TTG CAA AAC TTG ACT CAA CGC ATG 842
Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg Met
270 275 280

```
TAC TCT GTT GAA GTT ATT TTG GAT CTG CCT AAA TTC AAG ATT      884
Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile
                285                     290

GAA TCT GAA ATT AAT TTG AAT GAT CCT CTG AAA AAG TTG GGT      926
Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly
295                     300                     305

ATG TCT GAT ATG TTT GTT CCT GGA AAA GCT GAT TTC AAA GGA      968
Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly
    310                     315                     320

TTG CTT GAA GGA TCT GAT GAG ATG TTA TAT ATT TCT AAA GTA     1010
Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val
        325                     330                     335

ATT CAA AAA GCT TTC ATT GAA GTA AAT GAA GAA GGT GCT GAA     1052
Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu
            340                     345                 350

GCT GCA GCT GCC ACA GCG GTG CTT TTA GTA ACG GAA TCT TAT     1094
Ala Ala Ala Ala Thr Ala Val Leu Leu Val Thr Glu Ser Tyr
                355                     360

GTA CCT GAG GAA GTA TTC GAA GCT AAT CAT CCC TTT TAT TTT     1136
Val Pro Glu Glu Val Phe Glu Ala Asn His Pro Phe Tyr Phe
365                     370                     375

GCA CTC TAT AAA TCT GCA CAA AAT CCA GTA GAA TCT GAA AAT     1178
Ala Leu Tyr Lys Ser Ala Gln Asn Pro Val Glu Ser Glu Asn
    380                     385                     390

GAA AGC TCT GAA AAT GAA AAC CCT GAA AAT GTT GAA GTA CTA     1220
Glu Ser Ser Glu Asn Glu Asn Pro Glu Asn Val Glu Val Leu
        395                     400                     405

TT                                                          1222
```

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GGAAGATCTA TAAATATGCC GCGTCCTCAG TTTG 34

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

CGGAATTCTA ATTGGTAAAT CTCCCAGAG 29

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1155 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDs
(B) LOCATION: 1..1155

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
GTG TTT CTT TTT GTA TCA GTG TTA TTA CCA ATT TCA ACA ATG        42
Val Phe Leu Phe Val Ser Val Leu Leu Pro Ile Ser Thr Met
  1               5                  10

GCC GAT CCC CAG GAA TTG TCT ACA AGT ATT AAC CAG TTT GCT        84
Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala
 15                  20                  25

GGA AGC CTG TAC AAT ACA GTT GCT TCT GGC AAC AAA GAC AAT       126
Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn
     30                  35                  40

CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT CTA TCC CTG       168
Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu
         45                  50                  55

GTG TCA ATG GGA GCT GGT GGC AAT ACT GCC ACA CAA ATA GCT       210
Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala
             60                  65                  70

GCT GGT TTG CGT CAG CCT CAA TCA AAA GAA AAA ATT CAA GAT       252
Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp
                 75                  80

GAC TAC CAC GCA TTG ATG AAC ACT CTT AAT ACA CAA AAA GGT       294
Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln Lys Gly
 85                  90                  95

GTA ACT CTG GAA ATT GCC AAT AAA GTT TAT GTT ATG GAA GGC       336
Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu Gly
    100                 105                 110

TAT ACA TTA AAA CCC ACC TTC AAA GAA GTT GCC ACC AAC AAA       378
Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys
        115                 120                 125

TTC TTA GCT GGA GCA GAA AAC TTG AAC TTT GCC CAA AAT GCT       420
Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala
            130                 135                 140
```

```
GAA AGC GCT AAA GTT ATC AAC ACT TGG GTT GAA GAA AAA ACT      462
Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr
                145                 150

CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT GAT CTA GAC      504
His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp
155                 160                 165

CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC TTC AAG      546
Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys
    170                 175                 180

GGT CTT TGG GAG AAA CAA TTC AAA AAG GAA AAT ACC CAA GAC      588
Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp
        185                 190                 195

AAA CCT TTC TAT GTT ACT GAA ACA GAG ACA AAG AAT GTA CGA      630
Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn Val Arg
            200                 205                 210

ATG ATG CAC ATT AAG GAT AAA TTC CGT TAT GGA GAA TTT GAA      672
Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe Glu
                215                 220

GAA TTA GAT GCC AAG GCT GTA GAA TTG CCC TAC AGG AAC TCA      714
Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser
225                 230                 235

GAT TTG GCC ATG TTA ATC ATT TTG CCA AAC AGC AAA ACT GGT      756
Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly
    240                 245                 250

CTC CCC GCT CTT GAA GAA AAA TTA CAA AAT GTT GAT TTG CAA      798
Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln
        255                 260                 265

AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT TTG GAT      840
Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
            270                 275                 280

CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG AAT GAT      882
Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
                285                 290

CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT CCT GGA      924
Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly
295                 300                 305

AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT GAG ATG      966
Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
    310                 315                 320

TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT GAA GTA     1008
Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
        325                 330                 335

AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GCT ACC TTT     1050
Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Thr Phe
            340                 345                 350
```

```
ATG GTT ACC TAT GAA CTG GAG GTT TCC CTG GAT CTT CCC ACT     1092
Met Val Thr Tyr Glu Leu Glu Val Ser Leu Asp Leü Pro Thr
                355                 360

GTT TTT AAA GTC GAT CAT CCA TTC AAT ATT GTT TTG AAG ACA     1134
Val Phe Lys Val Asp His Pro Phe Asn Ile Val Leu Lys Thr
365                 370                 375

GGT GAT ACT GTT ATT TTT AAT                                 1155
Gly Asp Thr Val Ile Phe Asn
    380                 385
```

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
GGAAGATCTA TAAATATGAT TAACGCACGA CTT                        33
```

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
CCGGAATTCA TAGAGTTTGA ACTCGCCC                              28
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1065 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..1064

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```
AG TTT GCT GGA AGC CTG TAC AAT ACG GTT GCT TCT GGC AAC AAA   44
   Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys
     1               5                  10
```

GAC AAT CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT CTA 86
Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu
15 20 25

TCC CTG GTG TCA ATG GGA GCT GGT GGT AAT ACT GCC ACA CAA 128
Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln
30 35 40

ATA GCT GCT GGT TTA CGT CAG CCT CAA TCA AAA GAA AAA ATT 170
Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile
45 50 55

CAA GAT GAC TAC CAT GCA TTG ATG AAC ACT CTT AAT ACA CAA 212
Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln
60 65 70

AAA GGT GTA ACT CTG GAA ATT GCC AAC AAA GTT TAC GTT ATG 254
Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met
75 80

GAA GGC TAT ACA TTG AAA CCC ACC TTC AAA GAA GTT GCC ACC 296
Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr
85 90 95

AAC AAA TTC TTA GCT GGA GCA GAA AAC TTG AAC TTT GCC CAA 338
Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln
100 105 110

AAT GCT GAA AGC GCT AAA GTT ATC AAC ACT TGG GTT GAA GAA 380
Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu
115 120 125

AAA ACT CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT GAT 422
Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp
130 135 140

CTA GAC CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC 464
Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr
145 150

TTC AAG GGT CTT TGG GAG AAA CAA TTC AAG AAG GAA AAC ACT 506
Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr
155 160 165

CAA GAC AAA CCT TTC TAT GTT ACT GAA ACA GAG ACA AAG AAT 548
Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn
170 175 180

GTA CGA ATG ATG CAC ATT AAG GAT AAA TTC CGT TAT GGA GAA 590
Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu
185 190 195

TTT GAA GAA TTA GAT GCC AAG GCT GTA GAA TTG CCC TAC AGG 632
Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg
200 205 210

AAC TCA GAT TTG GCC ATG TTA ATC ATT TTG CCA AAC AGC AAA 674
Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys
215 220

```
ACT GGT CTC CCC GCT CTT GAA GAA AAA TTA CAA AAT GTT GAC      716
Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp
225                 230                 235

TTG CAA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT      758
Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile
    240                 245                 250

TTG GAT CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG      800
Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu
        255                 260                 265

AAT GAT CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT      842
Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val
            270                 275                 280

CCT GGA AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT      884
Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp
                285                 290

GAG ATG TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT      926
Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile
295                 300                 305

GAA GTA AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GGC      968
Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly
    310                 315                 320

ATT GTC ATG CTT GGT TGC TGT ATG CCA ATG ATG GAT CTT TCT     1010
Ile Val Met Leu Gly Cys Cys Met Pro Met Met Asp Leu Ser
        325                 330                 335

CCA GTA GTT TTT AAT ATT GAT CAC CCA TTT TAT TAC TCA TTG     1052
Pro Val Val Phe Asn Ile Asp His Pro Phe Tyr Tyr Ser Leu
            340                 345                 350

ATG ACT TGG GAT A                                           1065
Met Thr Trp Asp
```

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GCGGAATTCG ATCCCCAGGA ATTGTCTACA AGTATTAACC 40

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GCGAGATCTT TAAAGGGATT TAACACATCC ACTGAACAAA ACAG 44

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1070 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..1070

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
AG TTT GCT GGA AGC CTG TAC AAT ACG GTT GCT TCT GGC AAC AAA   44
   Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys
     1               5                  10

GAC AAT CTC ATC ATG TCC CCA TTG TCT GTA CAA ACT GTT CTA      86
Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu
 15                  20                  25

TCC CTG GTG TCA ATG GGA GCT GGT GGT AAT ACT GCC ACA CAA     128
Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln
     30                  35                  40

ATA GCT GCT GGT TTA CGT CAG CCT CAA TCA AAA GAA AAA ATT     170
Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile
         45                  50                  55

CAA GAT GAC TAC CAT GCA TTG ATG AAC ACT CTT AAT ACA CAA     212
Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln
             60                  65                  70

AAA GGT GTA ACT CTG GAA ATT GCC AAC AAA GTT TAC GTT ATG     254
Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met
                 75                  80

GAA GGC TAT ACA TTG AAA CCC ACC TTC AAA GAA GTT GCC ACC     296
Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr
 85                  90                  95

AAC AAA TTC TTA GCT GGA GCA GAA AAC TTG AAC TTT GCC CAA     338
Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln
    100                 105                 110

AAT GCT GAA AGC GCT AAA GTT ATC AAC ACT TGG GTT GAA GAA     380
Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu
        115                 120                 125

AAA ACT CAT GAC AAA ATT CAT GAT TTG ATC AAA GCC GGT GAT     422
Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp
            130                 135                 140
```

```
CTA GAC CAG GAT TCA AGA ATG GTT CTT GTC AAT GCA TTG TAC      464
Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr
                145                 150

TTC AAG GGT CTT TGG GAG AAA CAA TTC AAG AAG GAA AAC ACT      506
Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr
155                 160                 165

CAA GAC AAA CCT TTC TAT GTT ACT GAA ACA GAG ACA AAG AAT      548
Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn
    170                 175                 180

GTA CGA ATG ATG CAC ATT AAG GAT AAA TTC CGT TAT GGA GAA      590
Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu
        185                 190                 195

TTT GAA GAA TTA GAT GCC AAG GCT GTA GAA TTG CCC TAC AGG      632
Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg
            200                 205                 210

AAC TCA GAT TTG GCC ATG TTA ATC ATT TTG CCA AAC AGC AAA      674
Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys
                215                 220

ACT GGT CTC CCC GCT CTT GAA GAA AAA TTA CAA AAT GTT GAC      716
Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp
225                 230                 235

TTG CAA AAC TTG ACT CAA CGC ATG TAC TCT GTT GAA GTT ATT      758
Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile
    240                 245                 250

TTG GAT CTG CCT AAA TTC AAG ATT GAA TCT GAA ATT AAT TTG      800
Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu
        255                 260                 265

AAT GAT CCT CTG AAA AAG TTG GGT ATG TCT GAT ATG TTT GTT      842
Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val
            270                 275                 280

CCT GGA AAA GCT GAT TTC AAA GGA TTG CTT GAA GGA TCT GAT      884
Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp
                285                 290

GAG ATG TTA TAT ATT TCT AAA GTA ATT CAA AAA GCT TTC ATT      926
Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile
295                 300                 305

GAA GTA AAT GAA GAA GGT GCT GAA GCT GCA GCT GCC ACA GGC      968
Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly
    310                 315                 320

GTG ATG TTA ATG ATG CGT TGT ATG CCA ATG ATG CCA ATG GCC     1010
Val Met Leu Met Met Arg Cys Met Pro Met Met Pro Met Ala
        325                 330                 335

TTC AAT GCT GAG CAT CCA TTC CTG TAC TTC TTA CAC AGC AAA     1052
Phe Asn Ala Glu His Pro Phe Leu Tyr Phe Leu His Ser Lys
            340                 345                 350
```

AAT TCT GTT CTA TTC AAT 1070
Asn Ser Val Leu Phe Asn
355

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CGCAGATCTT TATTCAGTTG TTGGTTTAAC AAGACGACC 39

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

ATTAACCCTC ACTAAAG 17

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

ATAGGATCCC CAGGAATTGT C 21

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

GCGAGATCTC TAGTTATTAA TATTGGTTAA 30

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

GCGGAATTCT CATGGTGACT GAACGCG 27

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GCGGAATTCA ACAAAAGTGT GTTC 24

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala Gly
 1               5                  10

Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn Leu
 15                  20                  25

Ile Met
     30
```

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr
 1               5                  10
```

Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met
15 20 25

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr
1 5 10

Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro
15 20 25

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

GCGGAATTCT TATTTGGGAG ATATAACTCG 30

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CGCGAATTCT CATTCGACAA AATGACC 27

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

GCGGAATTCT TAAGGATTAA CGTGTTGAAC 30

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

GGAATTCTTA TTGCACAAAT CATCC 25

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 406 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

```
Ala Ile Val Gln His Ala Arg Leu Val Phe Leu Phe Val Ser
 1               5                  10

Val Leu Ile Pro Ile Ser Thr Met Ala Asp Pro Gln Glu Leu
 15                 20                  25

Ser Thr Ser Ile Asn Gln Phe Ala Gly Ser Leu Tyr Asn Thr
    30                  35                  40

Val Ala Ser Gly Asn Lys Asp Asn Leu Ile Met Ser Pro Leu
        45                  50                  55

Ser Val Gln Thr Val Leu Ser Leu Val Ser Met Gly Ala Gly
            60                  65                  70

Gly Asn Thr Ala Thr Gln Ile Ala Ala Gly Leu Arg Gln Pro
                75                  80

Gln Ser Lys Glu Lys Ile Gln Asp Asp Tyr His Ala Leu Met
 85                 90                  95

Asn Thr Leu Asn Thr Gln Lys Gly Val Thr Leu Glu Ile Ala
    100                 105                 110

Asn Lys Val Tyr Val Met Glu Gly Tyr Thr Leu Lys Pro Thr
        115                 120                 125

Phe Lys Glu Val Ala Thr Asn Lys Phe Leu Ala Gly Ala Glu
            130                 135                 140

Asn Leu Asn Phe Ala Gln Asn Ala Glu Ser Ala Lys Val Ile
                145                 150

Asn Thr Trp Val Glu Glu Lys Thr His Asp Lys Ile His Asp
155                 160                 165
```

```
Leu Ile Lys Ala Gly Asp Leu Asp Gln Asp Ser Arg Met Val
    170                 175                 180

Leu Val Asn Ala Leu Tyr Phe Lys Gly Leu Trp Glu Lys Gln
        185                 190                 195

Phe Lys Lys Glu Asn Thr Gln Asp Lys Pro Phe Tyr Val Thr
            200                 205                 210

Glu Thr Glu Thr Lys Asn Val Arg Met Met His Ile Lys Asp
                215                 220

Lys Phe Arg Tyr Gly Glu Phe Glu Glu Leu Asp Ala Lys Ala
225                 230                 235

Val Glu Leu Pro Tyr Arg Asn Ser Asp Leu Ala Met Leu Ile
    240                 245                 250

Ile Leu Pro Asn Ser Lys Thr Gly Leu Pro Ala Leu Glu Glu
        255                 260                 265

Lys Leu Gln Asn Val Asp Leu Gln Asn Leu Thr Gln Arg Met
            270                 275                 280

Tyr Ser Val Glu Val Ile Leu Asp Leu Pro Lys Phe Lys Ile
                285                 290

Glu Ser Glu Ile Asn Leu Asn Asp Pro Leu Lys Lys Leu Gly
295                 300                 305

Met Ser Asp Met Phe Val Pro Gly Lys Ala Asp Phe Lys Gly
    310                 315                 320

Leu Leu Glu Gly Ser Asp Glu Met Leu Tyr Ile Ser Lys Val
        325                 330                 335

Ile Gln Lys Ala Phe Ile Glu Val Asn Glu Glu Gly Ala Glu
            340                 345                 350

Ala Ala Ala Ala Thr Ala Val Leu Leu Val Thr Glu Ser Tyr
                355                 360

Val Pro Glu Glu Val Phe Glu Ala Asn His Pro Phe Tyr Phe
365                 370                 375

Ala Leu Tyr Lys Ser Ala Gln Asn Pro Val Glu Ser Glu Asn
    380                 385                 390

Glu Ser Ser Glu Asn Glu Asn Pro Glu Asn Val Glu Val Leu
        395                 400                 405
```

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 385 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Val Phe Leu Phe Val Ser Val Leu Leu Pro Ile Ser Thr Met
1 5 10

Ala Asp Pro Gln Glu Leu Ser Thr Ser Ile Asn Gln Phe Ala
15 20 25

Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys Asp Asn
30 35 40

Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu Ser Leu
45 50 55

Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln Ile Ala
60 65 70

Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile Gln Asp
75 80

Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln Lys Gly
85 90 95

Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met Glu Gly
100 105 110

Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr Asn Lys
115 120 125

Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln Asn Ala
130 135 140

Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu Lys Thr
145 150

His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp Leu Asp
155 160 165

Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr Phe Lys
170 175 180

Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr Gln Asp
185 190 195

Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn Val Arg
200 205 210

Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu Phe Glu
215 220

Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg Asn Ser
225 230 235

Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys Thr Gly
240 245 250

Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp Leu Gln
255 260 265

Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile Leu Asp
270 275 280

Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu Asn Asp
285 290

Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val Pro Gly
295 300 305

Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp Glu Met
310 315 320

Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile Glu Val
325 330 335

Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Thr Phe
340 345 350

Met Val Thr Tyr Glu Leu Glu Val Ser Leu Asp Leu Pro Thr
355 360

Val Phe Lys Val Asp His Pro Phe Asn Ile Val Leu Lys Thr
365 370 375

Gly Asp Thr Val Ile Phe Asn
380 385

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 354 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys
1 5 10

Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu
15 20 25

Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln
30 35 40

Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile
45 50 55

Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln
60 65 70

Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met
75 80

Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr
85 90 95

Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln
100 105 110

Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu
115 120 125

Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp
130 135 140

Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr
145 150

Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr
155 160 165

Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn
170 175 180

Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu
185 190 195

Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg
200 205 210

Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys
215 220

Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp
225 230 235

Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile
240 245 250

Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu
255 260 265

Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val
270 275 280

Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp
285 290

Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile
295 300 305

Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly
310 315 320

Ile Val Met Leu Gly Cys Cys Met Pro Met Met Asp Leu Ser
325 330 335

Pro Val Val Phe Asn Ile Asp His Pro Phe Tyr Tyr Ser Leu
340 345 350

Met Thr Trp Asp

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 356 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Phe Ala Gly Ser Leu Tyr Asn Thr Val Ala Ser Gly Asn Lys
1 5 10

Asp Asn Leu Ile Met Ser Pro Leu Ser Val Gln Thr Val Leu
15 20 25

Ser Leu Val Ser Met Gly Ala Gly Gly Asn Thr Ala Thr Gln
30 35 40

Ile Ala Ala Gly Leu Arg Gln Pro Gln Ser Lys Glu Lys Ile
45 50 55

Gln Asp Asp Tyr His Ala Leu Met Asn Thr Leu Asn Thr Gln
60 65 70

Lys Gly Val Thr Leu Glu Ile Ala Asn Lys Val Tyr Val Met
75 80

Glu Gly Tyr Thr Leu Lys Pro Thr Phe Lys Glu Val Ala Thr
85 90 95

Asn Lys Phe Leu Ala Gly Ala Glu Asn Leu Asn Phe Ala Gln
100 105 110

Asn Ala Glu Ser Ala Lys Val Ile Asn Thr Trp Val Glu Glu
115 120 125

Lys Thr His Asp Lys Ile His Asp Leu Ile Lys Ala Gly Asp
130 135 140

Leu Asp Gln Asp Ser Arg Met Val Leu Val Asn Ala Leu Tyr
145 150

Phe Lys Gly Leu Trp Glu Lys Gln Phe Lys Lys Glu Asn Thr
155 160 165

Gln Asp Lys Pro Phe Tyr Val Thr Glu Thr Glu Thr Lys Asn
170 175 180

Val Arg Met Met His Ile Lys Asp Lys Phe Arg Tyr Gly Glu
185 190 195

Phe Glu Glu Leu Asp Ala Lys Ala Val Glu Leu Pro Tyr Arg
200 205 210

Asn Ser Asp Leu Ala Met Leu Ile Ile Leu Pro Asn Ser Lys
215 220

Thr Gly Leu Pro Ala Leu Glu Glu Lys Leu Gln Asn Val Asp
225 230 235

Leu Gln Asn Leu Thr Gln Arg Met Tyr Ser Val Glu Val Ile
240 245 250

Leu Asp Leu Pro Lys Phe Lys Ile Glu Ser Glu Ile Asn Leu
255 260 265

Asn Asp Pro Leu Lys Lys Leu Gly Met Ser Asp Met Phe Val
270 275 280

```
Pro Gly Lys Ala Asp Phe Lys Gly Leu Leu Glu Gly Ser Asp
                285                 290

Glu Met Leu Tyr Ile Ser Lys Val Ile Gln Lys Ala Phe Ile
295                 300                 305

Glu Val Asn Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Gly
    310                 315                 320

Val Met Leu Met Met Arg Cys Met Pro Met Met Pro Met Ala
        325                 330                 335

Phe Asn Ala Glu His Pro Phe Leu Tyr Phe Leu His Ser Lys
            340                 345                 350

Asn Ser Val Leu Phe Asn
                355
```

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

What is claimed is:

1. An isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene.

2. An isolated nucleic acid molecule selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90; and a nucleic acid molecule comprising an allelic variant of a nucleic acid molecule comprising any of said nucleic acid sequences.

3. An isolated protein encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene.

4. An isolated flea protein selected from the group consisting of: a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97 and SEQ ID NO:98; and a protein encoded by an allelic variant of a nucleic acid molecule encoding a protein comprising any of said amino acid sequences.

5. A therapeutic composition that, when administered to an animal, reduces hematophagous ectoparasite infestation, said therapeutic composition comprising a protective compound selected from the group consisting of: an isolated flea serine protease inhibitor protein; a mimetope of a flea serine protease inhibitor protein; an isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene; an isolated antibody that selectively binds to a flea serine protease inhibitor protein; and an inhibitor of serine protease inhibitor activity identified by its ability to inhibit the activity of a flea serine protease inhibitor protein.

6. An inhibitor of serine protease inhibitor protein activity identified by its ability to inhibit the activity of a flea serine protease inhibitor protein.

7. A mimetope of a flea serine protease inhibitor protein identified by its ability to inhibit flea serine protease activity.

8. A method to reduce hematophagous ectoparasite infestation comprising administering to an animal a therapeutic composition comprising a protective compound selected from the group consisting of: an isolated flea serine protease inhibitor protein; a mimetope of a flea serine protease inhibitor protein; an isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene; an isolated antibody that selectively binds to a flea serine protease inhibitor protein; and an inhibitor of serine protease inhibitor activity identified by its ability to inhibit the activity of a flea serine protease inhibitor protein.

9. A method to produce a flea serine protease inhibitor protein, said method comprising culturing a cell transformed with a nucleic acid molecule that hybridizes under stringent hybridization conditions with a *Ctenocephalides felis* serine protease inhibitor gene.

10. A method to identify a compound capable of inhibiting flea serine protease inhibitor activity, said method comprising:

(a) contacting an isolated flea serine protease inhibitor protein with a putative inhibitory compound under conditions in which, in the absence of said compound, said protein has serine protease inhibitor activity; and

(b) determining if said putative inhibitory compound inhibits said activity.

11. A test kit to identify a compound capable of inhibiting flea serine protease inhibitor activity, said test kit comprising an isolated flea serine protease inhibitor protein having serine protease inhibitor activity and a means for determining the extent of inhibition of said activity in the presence of a putative inhibitory compound.

12. The nucleic acid molecule of Claim 1, wherein said *Ctenocephalides felis* serine protease inhibitor gene comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71,SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90.

13. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule comprises a nucleic acid sequence that encodes a serine protease inhibitor protein.

14. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is a flea nucleic acid molecule.

15. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is selected from the group consisting of *Ctenocephalides*, *Ceratophyllus*, *Diamanus*, *Echidnophaga*, *Nosopsyllus*, *Pulex*, *Tunga*, *Oropsylla*, *Orchopeus* and *Xenopsylla* nucleic acid molecules.

16. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is selected from the group consisting of *Ctenocephalides felis*, *Ctenocephalides canis*, *Ceratophyllus pulicidae*, *Pulex irritans*, *Oropsylla (Thrassis) bacchi*, *Oropsylla*

(Diamanus) montana, *Orchopeus howardi*, *Xenopsylla cheopis* and *Pulex simulans* nucleic acid molecules.

17. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule comprises a *Ctenocephalides felis* nucleic acid molecule.

18. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule hybridizes under stringent hybridization conditions with a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:69 and SEQ ID NO:71.

19. The invention of Claims 1 or 9, wherein said nucleic acid molecule is selected from the group consisting of $nfSPI1_{1584}$, $nfSPI1_{1191}$, $nfSPI1_{376}$, $nfSPI2_{1358}$, $nfSPI2_{1197}$, $nfSPI2_{376}$, $nfSPI3_{1838}$, $nfSPI3_{1260}$, $nfSPI3_{391}$, $nfSPI4_{1414}$, $nfSPI4_{1179}$, $nfSPI4_{376}$, $nfSPI5_{1492}$, $nfSPI5_{1194}$, $nfSPI5_{376}$, $nfSPI6_{1454}$, $nfSPI6_{1191}$, $nfSPI6_{376}$, $nfSPI7_{549}$, $nfSPI8_{549}$, $nfSPI9_{581}$, $nfSPI10_{654}$, $nfSPI11_{670}$, $nfSPI12_{706}$, $nfSPI13_{623}$, $nfSPI14_{731}$, $nfSPI15_{685}$, $nfSPI3_{1222}$, $nfSPI6_{1155}$, $nfSPI2_{1065}$, $nfSPI4_{1070}$, $nfSPIC4{:}V7_{1168}$, $nfSPIC4{:}V8_{1222}$, $nfSPIC4{:}V9_{1174}$, $nfSPIC4{:}V10_{1159}$, $nfSPIC4{:}V12_{1171}$, $nfSPIC4{:}V13_{1171}$, and $nfSPIC4{:}V15_{1179}$.

20. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33. SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:66, SEQ ID

NO:66, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78, SEQ ID NO:81, a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; and a nucleic acid molecule comprising an allelic variant of any of said nucleic acid molecules.

21. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule encodes a protein comprising an amino acid sequence that is at least about 40% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:8, SEQ ID NO:14, SEQ ID NO:20, SEQ ID NO:26, SEQ ID NO:32, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90.

22. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule hybridizes under stringent hybridization conditions with a nucleic acid sequence encoding a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90.

23. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence that encodes a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90; and a nucleic acid molecule comprising an allelic variant of a nucleic acid sequence encoding a protein comprising any of said amino acid sequences.

24. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule comprises an oligonucleotide.

25. A recombinant molecule comprising a nucleic acid molecule as set forth in Claim 1 operatively linked to a transcription control sequence.

26. A recombinant virus comprising a nucleic acid molecule as set forth in Claim 1.

27. A recombinant cell comprising a nucleic acid molecule as set forth in Claim 1.

28. The protein of Claim 3, wherein said nucleic acid molecule hybridizes under stringent hybridization conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:21, SEQ ID NO:27, and SEQ ID NO:33, SEQ ID NO:47, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:56, SEQ ID NO:59, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:68 and SEQ ID NO:71.

29. The protein of Claim 3, wherein said protein, when administered to an animal, elicits an immune response against a serine protease inhibitor protein.

30. The protein of Claim 3, wherein said protein is a flea protein.

31. The protein of Claim 3, wherein said protein is selected from the group consisting of: a protein encoded by a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:19, SEQ IS NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:54, SEQ ID NO:57, SEQ ID NO:60, SEQ ID NO:63, SEQ IS NO:66, SEQ ID NO:69, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:78 and SEQ ID NO:81; and a protein encoded by a nucleic acid molecule comprising an allelic variant of a nucleic acid molecule comprising any of said nucleic acid sequences.

32. The protein of Claim 3, wherein said protein is selected from the group consisting of: a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID

NO:30, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:70, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97 and SEQ ID NO:98; and a protein encoded by an allelic variant of a nucleic acid molecule encoding a protein comprising any of said amino acid sequences.

33. An isolated antibody that selectively binds to a protein as set forth in Claims 3 or 4.

34. The invention of Claims 5 or 8, wherein said flea serine protease inhibitor protein comprises a peptide of a flea serine protease inhibitor protein capable of inhibiting serine protease activity.

35. The invention of Claims 5 or 8, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant, and a carrier.

36. The invention of Claims 5 or 8, wherein said composition further comprises a compound that reduces hematophagous ectoparasite burden by a method other than by reducing flea serine protease inhibitor activity.

37. The invention of Claims 5 or 8, wherein said protective compound is selected from the group consisting of a naked nucleic acid vaccine, a recombinant virus vaccine and a recombinant cell vaccine.

38. The invention of Claims 5 or 6 or 8, wherein said inhibitor of serine protease inhibitor protein activity comprises a substrate analog of a flea serine protease inhibitor protein.

39. The invention of Claims 6, wherein said inhibitor comprises a peptidomimetic compound.

40. The mimetope of Claim 7, wherein said mimetope comprises a peptidomimetic compound.

41. The method of Claim 8, wherein said hematophagous ectoparasite is a flea.

42. The method of Claim 8, wherein said flea is of a genus selected from the group consisting of *Ctenocephalides, Ceratophyllus, Diamanus, Echidnophaga, Nosopsyllus, Pulex, Tunga, Oropsylla, Orchopeus* and *Xenopsylla.*

43. The method of Claim 8, wherein said flea is of a species selected from the group consisting of *Ctenocephalides felis, Ctenocephalides canis, Ceratophyllus pulicidae, Pulex irritans, Oropsylla (Thrassis) bacchi, Oropsylla (Diamanus) montana, Orchopeus howardi, Xenopsylla cheopis* and *Pulex simulans.*

44. The method of Claim 8, wherein said animal is selected from the group consisting of adult hematophagous ectoparasites, hematophagous ectoparasite larvae and animals susceptible to hematophagous ectoparasite infestation.

45. The method of Claim 8, wherein said animal is selected from the group consisting of adult fleas, flea larvae and animals susceptible to flea infestation.

46. The method of Claim 8, wherein said animal is selected from the group consisting of mammals and birds.

47. The method of Claim 8, wherein said animal is selected from the group consisting of felids and canids.

48. The method of Claim 9, wherein said cell is selected from the group consisting of *E.coli*HB:pλP_R-nfSPI2$_{1139}$, *E.coli*HB:pλP_R-nfSPI3$_{1179}$, *E.coli*HB:pλP_R-nfSPI4$_{1140}$, *E.coli*HB:pλP_R-nfSPI5$_{1492}$, *E.coli*HB:pλP_R-nfSPI6$_{1136}$,*E.coli*:pλP_R-nfSPIC4:V7$_{1168}$, *E.coli*:pλP_R-nfSPIC4:V8$_{1222}$, *E.coli*:pλP_R-nfSPIC4:V9$_{1174}$, *E.coli*:pλP_R-nfSPIC4:V10$_{1159}$, *E.coli*:pλP_R-nfSPIC4:V12$_{1171}$, *E.coli*:pλP_R-nfSPIC4:V13$_{1171}$, *E.coli*:pλP_R-nfSPIC4:V15$_{1179}$, *S. frugiperda*:pVL-nfSPI3$_{1222}$, *S. frugiperda*:pVL-nfSPI6$_{1155}$, *S. frugiperda*:pAcG-nfSPI2$_{1065}$ and *S. frugiperda*:pAcG-nfSPI4$_{1070}$.

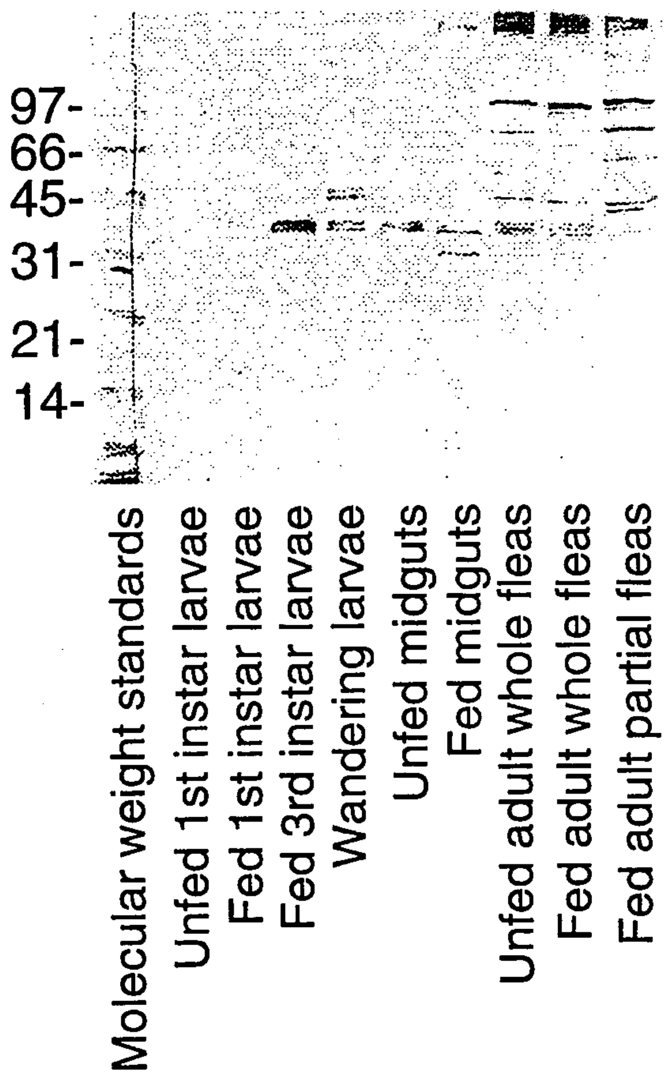
97-
66-
45-
31-
21-
14-
Molecular weight standards
Unfed 1st instar larvae
Fed 1st instar larvae
Fed 3rd instar larvae
Wandering larvae
Unfed midguts
Fed midguts
Unfed adult whole fleas
Fed adult whole fleas
Fed adult partial fleas

Fig. 1